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Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomized clinical trials

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Abstract

Objective: We studied the safety and efficacy of hydroxychloroquine (HCQ) as pre-exposure prophylaxis for COVID-19 in healthcare workers (HCWs), using a meta-analysis of randomized controlled trials.

Data Sources: PubMed, EMBASE, EBSCO, and Cochrane databases were searched to identify randomized trials studying HCQ.

Study Selection: Five randomized controlled trials (RCTs) were identified (n=3,672 participants).

Data Extraction and Synthesis: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review and meta-analysis between HCQ and placebo using a Bayesian random-effects model. A *pre-hoc* statistical analysis plan was written, and the review protocol was registered at PROSPERO (CRD42021285093)

Main Outcomes: The primary efficacy outcome was polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection and the primary safety outcome was incidence of adverse events. The secondary outcome included clinically suspected SARS-CoV-2 infection.

Results: Compared with placebo, HCWs randomized to hydroxychloroquine (HCQ) had no significant difference in PCR-confirmed SARS-CoV-2 infection (odds ratio [OR] 0.60, 95% credible interval [CI]: 0.24, 1.28), clinically suspected SARS-CoV-2 infection (OR 0.76, 95% CI: 0.48, 1.24), or adverse events (OR 1.46, 95% CI: 0.87, 2.22).

Conclusions and Relevance: Our meta-analysis of five RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs found that HCQ does not significantly reduce the risk of confirmed or clinically suspected SARS-CoV-2 infection or significantly increase adverse events compared with placebo.

INTRODUCTION

Early during the SARS-CoV-2 pandemic, based on *in vitro* antiviral activity of both chloroquine and hydroxychloroquine against SARS-CoV-2 [1-3], clinicians considered use of hydroxychloroquine (HCQ) for treatment and prevention of SARS-CoV-2 infection and the associated disease, COVID-19. While there are now published randomized controlled trials of HCQ for the treatment of COVID-19 in the inpatient and outpatient setting [4 5], there remains a lack of adequately powered randomized controlled trials of HCQ for the pre-exposure prophylaxis (PrEP) of SARS-CoV-2 infection. A number of PrEP studies were planned early in the pandemic; however, several never opened to enrollment and those that did open were closed early without reaching full accrual due to the rapidly changing landscape of preventative therapies, including vaccines, and a significant shift in public opinion of HCQ as a medical intervention for SARS-CoV-2.

Yet, as vaccination access remains insufficient globally [6], studying the pre-exposure prophylaxis potential for a drug with a known safety profile is crucial to protect people at high risk of exposures, such as healthcare workers (HCWs) [7 8]. Two large randomized, placebo-controlled trials testing the safety and efficacy of HCQ as pre-exposure prophylaxis for COVID-19 in HCWs, PATCH [9] and Minnesota (MN)-COVID-PREP [10], showed potential for a modest benefit of HCQ but were both underpowered, if a modest effect exists. In addition, more trials [11-13] studying HCQ as pre-exposure prophylaxis of COVID-19 in HCWs have since been completed and with similar limitations.

To address the most common limitation, inadequate power to show a modest effect, we conducted a formal meta-analysis of pre-exposure prophylactic HCQ studies in HCWs. We conducted a systematic search for clinical trials of pre-exposure prophylactic use of HCQ against

infection of SARS-CoV-2 in HCWs, thoroughly compared similarities and differences in characteristics of the identified studies and performed a Bayesian meta-analysis to combine results of the trials.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review and meta-analysis[14]. A statistical analysis plan was written in advance and the review protocol was registered at PROSPERO (CRD42021285093).

Search strategy and information sources

We searched PubMed/Medline, Ovid/Embase, EBSCO/CINAHL, and Cochrane databases from database inception through the final search date October 11, 2021. We used keywords related to COVID-19, HCQ, and prophylaxis. The full search strategies are provided in eTable 1. Unpublished data from eligible randomized controlled trials listed on ClinicalTrials.gov and other relevant information were obtained by contacting the study authors and principal investigators.

Eligibility criteria and study selection

The eligibility criteria included phase II or phase III randomized controlled trials (RCTs) of hydroxychloroquine for use as pre-exposure prophylaxis in HCWs with moderate to high risk of exposure. We excluded observational studies, crossover trials, studies where the method of allocation to treatment was not truly random, duplicate studies, and non-original data studies. No language, publication date, or publication status restrictions were applied. References of prior

systematic reviews and meta-analyses were also screened for related studies. Study selection involved screening of titles and abstracts followed by full-text evaluation of possible eligible studies.

Data collection process

Each of the selected studies were independently reviewed by two reviewers (AF, MH, or HH). We extracted data on the study design, baseline characteristics, interventions, and outcomes. Any disagreements of collected information between reviews were reconciled through discussion by all three reviewers.

Outcome measures

The primary efficacy outcome for the meta-analysis was laboratory confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) test and the primary safety outcome was incidence of adverse events (Table 1). The secondary efficacy outcome was suspected or probable SARS-CoV-2 infection. Included studies had the following outcome definitions: (1) laboratory confirmed SARS-CoV-2 infection defined as COVID-19 like symptoms and positive SARS-CoV-2 PCR and (2) suspected or probable SARS-CoV-2 infection defined as COVID-19 like symptoms but lack of confirmatory PCR testing.

Table 1. Treatment strategies, adherence, trial-defined primary outcome, and follow-up time in each trial

Trial (NCT ID)	Trial-defined primary outcome	Follow-up	Treatment group	Randomized treatment assignment	Randomized sample size
HERO-HCQ (NCT04334148)	Confirmed (by NP swab PCR) or suspected COVID-19 infection	60 days	HCQ	HCQ 600 mg BID loading dose for Day 1, followed by 400 mg QD for 29 days	683

	through 30 days		Placebo	Placebo	676
PATCH (NCT04329923)	COVID-19 infection as determined by positive NP swab over 8 weeks	56 days (8 weeks)	HCQ	HCQ 600mg daily for 60 days	64
			Placebo	Placebo	61
MN-COVID-PREP (NCT04328467)	COVID-19 free survival time by lab confirmed or probable illness	84 days (12 weeks)	HCQ[1]	HCQ loading doses (400mg twice 6-8hrs apart) followed by 400mg once weekly or 400mg twice weekly for 84 days	989
			Placebo	Placebo	494
Rojas-Serrano et al. (NCT04318015)	Time to symptomatic respiratory infection with a positive COVID RT PCR over 60 days	60 days	HCQ	HCQ 200 mg daily for 60 days	62
			Placebo	Placebo	65
WHIP (NCT04341441)	Lab confirmed cases of COVID-19 determined by either IgM and IgG serology in blood sample or RT-PCR test results Confirmed new cases of COVID-19	56 days (8 weeks)	HCQ[2]	HCQ 400 mg loading dose for Day 1, followed by 200 mg daily or 400 mg weekly on the same day of each week for 56 days	387
			Placebo	Placebo	191

HCQ=Hydroxychloroquine

[1] HCQ group in the MN-COVID-PREP study includes participants taking 400 mg once weekly or 400 mg twice weekly.

[2] HCQ group in the WHIP study includes participants taking 200 mg daily or 400 mg weekly.

Treatment assignment

Our meta-analysis did not study HCQ dosing specific effects. For studies randomizing participants to more than one HCQ arm with different doses, all HCQ arms were merged and considered as a single HCQ arm. For example, the MN-COVID-PREP and WHIP studies each had HCQ arms with weekly or twice weekly dosing, thus these two arms were combined as a single HCQ arm for the meta-analysis (Table 1).

Risk of bias within individual studies

Two independent reviewers (AF, HH) assessed the risk of bias (low, intermediate, high) of the included studies using the Cochrane's Collaboration tool [15] (eTable 2).

Statistical analysis

Bayesian logistic regression meta-analysis models under two assumptions (fixed effect and random effects) were fitted to estimate the odds ratio of having an outcome between hydroxychloroquine and placebo [16]. The fixed effect model assumes that the odds ratio is constant across studies, while the random effects model accounts for heterogeneity in the odds ratios across studies. To assess and compare the goodness-of-fit of the fitted fixed and random effects models, we calculated the Watanabe-Akaike information criterion [17]. In the Bayesian models, we assigned non-informative prior distributions as no prior information was available. The odds ratios and the associated 95% confidence intervals were estimated using Markov chain Monte Carlo (MCMC) algorithms. In addition, we calculated Bayesian posterior probabilities of the odds ratio smaller than 1 or 0.5 for the primary efficacy outcome, and greater than 2 for the safety outcome [18]. The standard deviation of the random effects and I^2 [19] were estimated to quantify the between-study heterogeneity, where small values of both metrics indicate little heterogeneity. All analyses were conducted using the `rstan` package (version 2.21.2)[20] in R 4.0.2 [21]. We used two parallel chains, where each chain consists of 50,000 samples after a 25,000-sample burn-in. We checked convergence of the MCMC chains for all model parameters using trace plots and Gelman-Rubin diagnostic statistics [22].

Patient and public involvement

No patient involved.

RESULTS

Search results

Our database search resulted in 164 unique studies after excluding duplicates. Of those, 161 studies were screened out due to irrelevance based on title and abstract screening. Three studies were assessed in full-text for eligibility and they met the inclusion criteria (Figure 1). Of those, two trials, conducted by the University of Pennsylvania (NCT04329923, denoted by PATCH) [9] and the University of Minnesota (NCT04328467, denoted by MN-COVID-PREP) [10], recruited healthcare workers (HCWs) while the third cluster-randomized trial, conducted by the National University of Singapore (NCT04446104), recruited non-HCWs[23] was excluded from the meta-analysis. Additionally, we identified three eligible trials via ClinicalTrials.gov that were completed but had not yet been published in peer-reviewed journals and included in the meta-analysis. These three studies recruited HCWs and were conducted by Duke University (NCT04334148, denoted by HERO-HCQ)[11], the National Institute of Respiratory Diseases of Mexico (NCT04318015, denoted by Rojas-Serrano et al.) [12], and the Henry Ford Health System (NCT04341441, denoted by WHIP)[13]. As a result, a total of five studies in a population consisting of HCWs were identified. The secondary efficacy outcome of suspected or probable SARS-CoV-2 infection was reported by HERO-HCQ, MN-COVID-PREP, and WHIP studies.

Study and patient characteristics

Study design, population, treatment strategies, and key characteristics are presented in Table 1 and eTable 3. A total of 3,672 randomized participants (2,185 randomized to HCQ) from the 5 studies were included in the meta-analysis. The five studies defined HCWs broadly and included first responders (emergency medical services, fire, and police). The follow-up duration of the 5

studies ranged from 56 days to 84 days. The HCQ dosing scheme varied across studies, including daily dosing ranging from 200 to 600mg daily with or without a loading dose and once or twice weekly dosing. The duration of therapy also varied across studies with a range of 30 to 84 days (Table 1). The trial-specific definitions of primary outcome and adverse events are comparable across trials (Table 1, eTable 4).

Baseline characteristics by randomized treatment assignment are reported (eTable 5). The HERO-HCQ, MN-COVID-PREP, and WHIP studies had average age between 40 and 45, while PATCH and Rojas-Serrano et al. included relatively younger participants with average age between 31 and 34 years. The aggregate proportion of women within each study varied across the 5 trials, with a range from 51% to 69%. In addition, the PATCH and Rojas-Serrano et al. studies had smaller sample size compared with the other three studies and showed a difference in female ratio between placebo and HCQ groups. In the HERO-HCQ, PATCH, MN-COVID-PREP, and WHIP studies, over 80% of study participants were white. The PATCH and MN-COVID-PREP studies had high proportions of HCWs working in an emergency department (56% and 41%, respectively) and the PATCH study had a high proportion of nurses (67%).

Treatment adherence was assessed by two methods, self-reported adherence and/or pill count at the end of the study. MN-COVID-PREP additionally conducted remote blood sampling to verify HCQ concentrations in a subset. Adherence varied significantly across the studies, with a low proportion of approximately 52% in the Rojas-Serrano et al. study and 97-98% in the PATCH study.

Results of meta-analysis

Overall, 1.2% (45/3672) developed PCR-confirmed SARS-CoV-2 infection and 5.8% (200/3420) developed suspected COVID-19 that was not laboratory confirmed. Since the goodness-of-fit assessment using Watanabe-Akaike information criterion concluded that the random effects meta-analysis model was as good as or better than the fixed effect meta-analysis model for all outcomes, we reported the results under the random effects model. Compared with placebo, HCWs randomized to HCQ had numerically lower rate of PCR-confirmed SARS-CoV-2 infection cases (odds ratio [OR] 0.60, 95% credible interval [CI]: 0.24, 1.28), and suspected or probable SARS-CoV-2 infection cases (OR 0.76, 95% CI: 0.48, 1.24). Participants treated with HCQ had a numerically higher rate of adverse events (OR 1.46, 95% CI: 0.87, 2.22) (Figure 2). None of these odds ratios were statistically significant. The outcome data used in our analyses are presented in eTable 6.

The Bayesian posterior probabilities of the odds ratio less than 1 for the confirmed SARS-CoV-2 infection outcome (i.e., the probability of HCQ favoring over placebo) was 0.92, while the posterior probability of odds ratio less than 0.5 (i.e., the probability that the odds of having a confirmed SARS-CoV-2 infection outcome in HCQ is less than a half of the odds in placebo) was 0.32. The posterior probability of the odds ratio greater than 2 for the adverse event outcome (i.e., the probability that the odds of having an adverse event in HCQ is greater than twice of the odds in placebo) was 0.05.

Our meta-analysis showed little or moderate variability of effect estimates across studies with I^2 value of 0%, 0%, and 55%, and the estimated standard deviation of the random effects of 0.30,

0.25, and 0.38 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection, and adverse event outcomes, respectively.

DISCUSSION

Understanding the pre-exposure prophylactic effect of HCQ against COVID-19 remains relevant, as its use continues, particularly in the international setting [24 25]. Our meta-analysis of the five RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in 3672 HCWs found that HCQ did not have a statistical association with fewer confirmed or suspected/probable SARS-CoV-2 infection cases compared with placebo. While the odds ratios of the studies and the meta-analysis all favor HCQ, the confidence intervals remain wide suggesting low confidence in the true point estimate. Furthermore, in this population, COVID-19 events rates were low, particularly for the most relevant PCR-confirmed infection outcome. The low event rate raises further concern for the uncertainty of these outcomes. Thus, if there is a minimal effect, the absolute benefit would be low. To gain more certainty, a very large study would need to be done and this is difficult to support now due to availability of highly effective vaccines. The safety profile of HCQ in the outpatient setting is well understood [26]. In these outpatient studies there was no significant difference in adverse events in the HCQ versus the placebo arm, confirming the well-known safety profile of HCQ.

Our findings can be applied to HCWs but should not be generalized to a broader population. Our systematic search found only one published RCT of pre-exposure prophylaxis from Singapore that was not in HCW. This study showed a significant reduction in the risk of COVID-19 infection in the HCQ arm when compared with the comparator arm, vitamin C. However, this

study showed moderate risk of bias as it used an open-label cluster-randomization design, the Institutional Review Board excluded higher risk persons from the hydroxychloroquine arm only, and the participants may not be representative of a general population due to the communal living environment.

A prior meta-analysis [27] investigated pre-exposure (two RCTs included) and post-exposure (three RCTs included) prophylactic effects of HCQ and found insignificant effects on SARS-CoV-2 infection and adverse events, similar to ours. For the pre-exposure prophylactic effects, our meta-analysis includes three additional RCTs, resulting in the most up-to-date, systematic, and comprehensive evidence.

Although a meta-analysis allows for combining evidence from multiple studies in a principled way, our meta-analysis has limitations. First, our analysis did not evaluate effects of different HCQ doses and combined two weekly dosing HCQ arms using different doses in each of MN-COVID-PREP and WHIP studies. The five RCTs included in our meta-analysis studied five different dosing schemes and a meta-analysis using aggregate-level data is not a sufficient source to study dosing effects. Second, detailed subgroup analyses were not conducted due to limited information. Individual-level data are required to study both dosing and subgroup effects.

Our meta-analysis of five RCTs investigating safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs provides the most up-to-date evidence on HCQ. We found that HCQ does not reduce the risk of confirmed or probable SARS-CoV-2 infection or adverse events compared

with placebo. Hydroxychloroquine should not be used for pre-exposure prophylaxis in the HCW population.

Contributors

All authors fulfill the ICMJE criteria for authorship. Drs. Hong, Naggie, Rajasingham, and Anstrom designed the study. Drs. Hong and Friedland and MS Hu collected and analyzed the data. Drs. Hong, Naggie, and Rajasingham wrote the manuscript and all authors provided critical review. All authors approved and decided to submit the paper for publication.

Competing interests

All authors except Dr. Abella reported no financial relationship with commercial interest. Dr. Abella have received NIH funds for COVID-19 related research, and holds equity in VOC Health, a start-up company that is developing novel covid testing.

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Data sharing statement

The data are presented in eTable 6.

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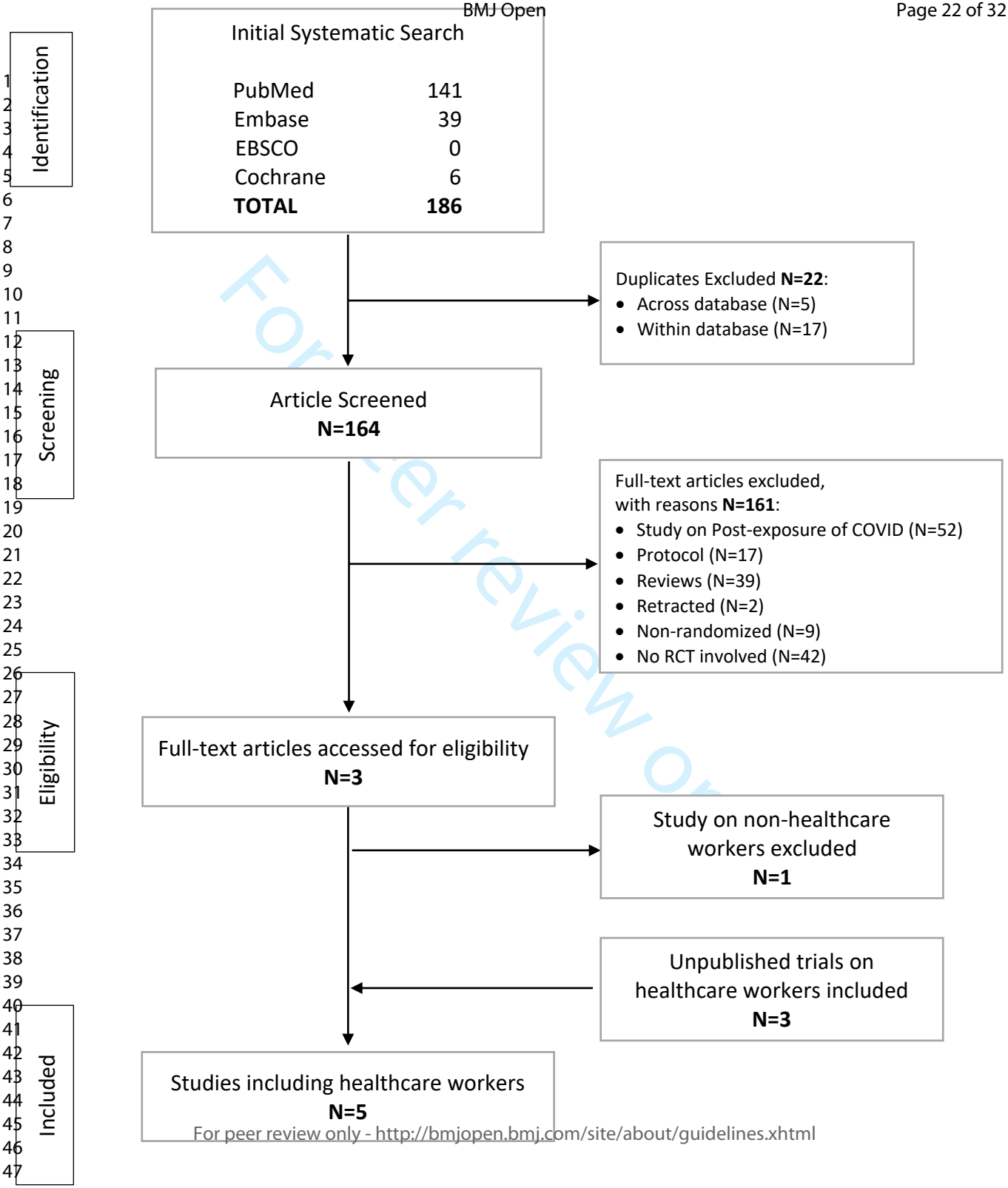
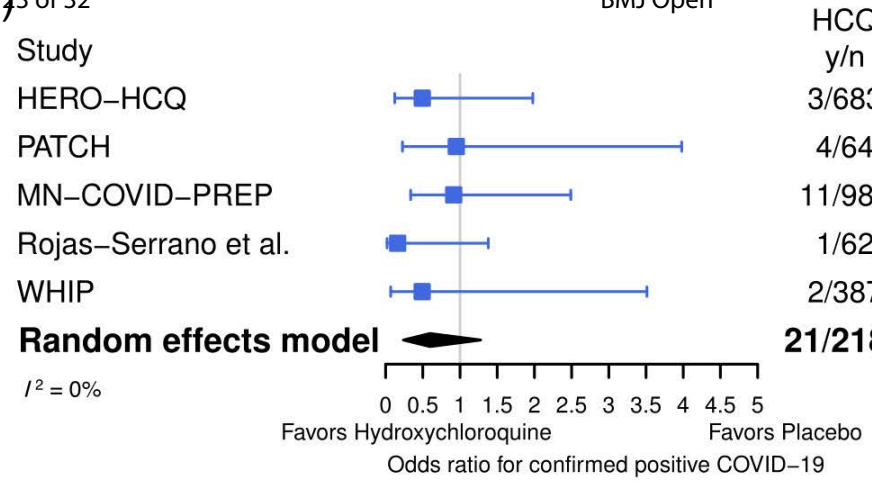
Figure Legends

Figure 1. Flowchart of literature review

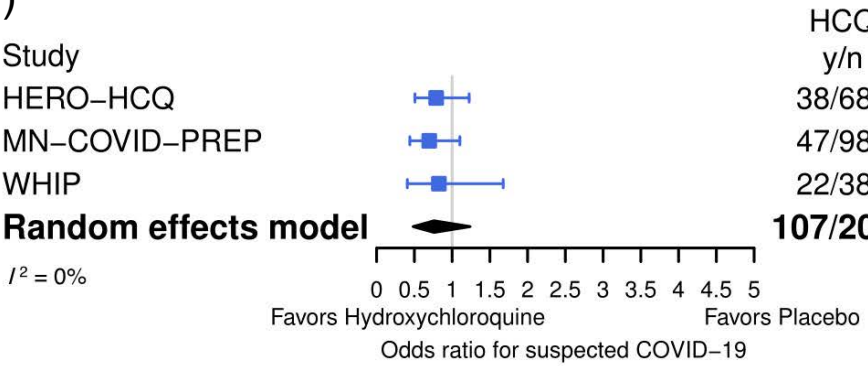
Figure 2. Forest plots of the meta-analysis results showing the number of events (y), sample size (n), posterior median of odds ratios, and the associated 95% credible intervals comparing HCQ versus placebo for (a) lab-confirmed positive COVID-19, (b) suspected COVID-19, and (c) adverse events.



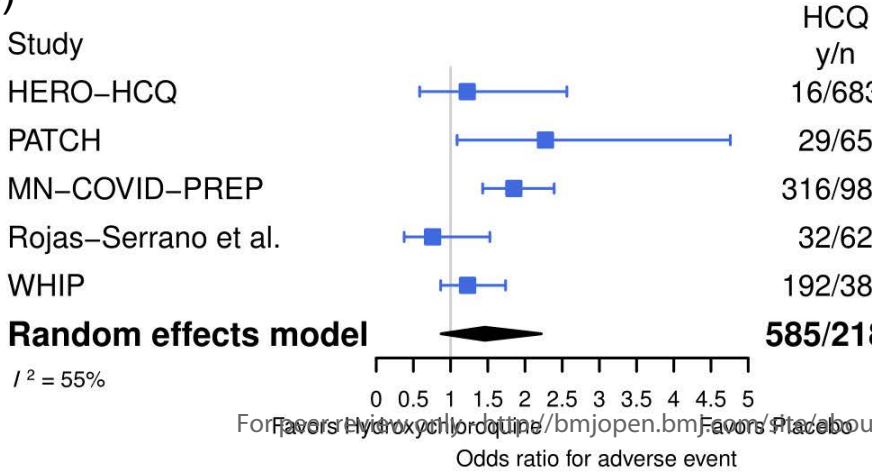
(a)



(b)



(c)



Supplementary Materials

CONTENTS

eTable 1. Search code that was used to identify publications as of October 11, 2021

PubMed search

#1	((covid[Title/Abstract]) OR (coronavirus[Title/Abstract])) OR (sars-cov[Title/Abstract])
#2	(hcq[Title/Abstract]) OR (hydroxychloro[Title/Abstract])
#3	(prophyl[Title/Abstract]) OR (Prep[Title/Abstract])
#4	(randomized clinical trial[Publication Type]) OR (controlled clinical trial[Publication Type]) OR (randomized[Title/Abstract]) OR (randomised[Title/Abstract])
#5	#1 AND #2 AND #3 AND #4

Embase search

#1	covid:ab,ti OR coronavirus:ab,ti OR 'sars cov':ab,ti
#2	prep:ab,ti OR prophylaxis:ab,t
#3	'randomized controlled trial':ab,ti OR 'randomized clinical trial':ab,ti
#4	hydroxychloroquine:ab,ti OR hcq:ab,ti
#5	#1 AND #2 AND #3 AND #4

Ebsco search

S1	TX covid OR TX coronavirus OR TX sars-cov
S2	TX hydroxychloroquine OR TX HCQ
S3	TX prep OR TX prophyl
S4	TX randomized clinical trial OR TX controlled clinical trial
S5	S1 AND S2 AND S3 AND S4

Cochrane search

#1	(covid):ti,ab,kw OR (coronavirus):ti,ab,kw OR ("SARS-CoV"):ti,ab,kw (Word variations have been searched)
#2	("hydroxychloroquine"):ti,ab,kw OR (hcq):ti,ab,kw
#3	(prophyl):ti,ab,kw OR (prep):ti,ab,kw
#4	("randomized clinical trial"):pt OR (controlled clinical trial):pt OR (randomized):ti,ab,kw OR (randomised):ti,ab,kw
#5	#1 AND #2 AND #3
#6	#4 AND #5

eTable 2. Risk of bias of included trials using the Cochrane risk assessment tool. Green circle is for low risk and yellow circle is for some concerns

	HERO-HCQ NCT04334148	PATCH NCT04329923	MN-COVID-PREP NCT04328467	Rojas-Serrano et al. NCT04318015	WHIP NCT04341441
Selection bias (Randomization process)					
Performance bias (Deviations from the intended interventions)					
Attrition bias[1] (Missing outcome data)					
Reporting bias (Measurement of the outcome)					
Other sources of bias (Selection of the reported result)					

[1] All studies but the Mexico study reported minimal loss to follow-up (<10%). The Mexico study reported 18% (25/130) lost to follow-up and additional 12% (16/130) discontinued the intervention.

eTable 3. Characteristics of included trials

	HERO-HCQ NCT04334148	PATCH NCT04329923	MN-COVID-PREP NCT04328467	Rojas-Serrano et al. NCT04318015	WHIP NCT04341441
N (randomization)	1360	132	1496	130	624
Study start date[1]	4/22/2020	4/9/2020	4/6/2020	4/21/2020	4/10/2020
Study completion date[2]	1/9/2021	11/13/2020	7/13/2020	3/31/2021	12/14/2020
Occupation	HCWs at risk of COVID exposure through work in the ICU, emergency department, emergency services, respiratory services or COVID unit	HCWs (Physicians, nurses, certified nursing assistants, emergency technicians, respiratory therapists) eligible working >20 hrs/week	HCWs (physicians, nurses, emergency medical technicians) with direct contact with COVID patients including emergency department and ICU setting, first responders and performing aerosol generating procedures	HCWs (nurses, nursing aids, cleaning staff, orderlies, respiratory therapists and physicians) taking care of hospitalized patients with COVID	HCW, first responders and correlational/law officers, nursing home workers, medical students, public transit workers, household family members of HCW in Michigan and Ohio
Sites	34 sites across the US	2 tertiary urban hospitals	Multiple sites nationwide across US and Canada	Single site (National Institute of Respiratory Diseases of Mexico)	Multiple sites at Michigan in the US
Randomization	Yes (Phase III)	Yes (Phase II)	Yes (Phase III)	Yes (Phase III)	Yes (Phase III)
Trial type	Double-blinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	No weight requirement	<40kg excluded	<50kg excluded	N/A
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Excluded	Excluded	Excluded	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Included	Exclude
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Included	
Significant renal disease (stage IV or greater)	Excluded	Included	Excluded	Excluded	Exclude
Pregnant/breastfeeding	Included	Excluded	Included in US, Excluded in Canada	Excluded	Exclude
Medication					
Qtc prolonging medications	Excluded	Excluded	Excluded	Included	Exclude
Use of other medications with significant drug interactions	Included	Excluded	Excluded	Included	N/A
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine or azithromycin)	Any treatment for COVID-19 within 14 days excluded	Current use of HCQ or chloroquine excluded	HCQ or chloroquine within 30 days excluded	Chronic use of HCQ included
COVID-19 related criteria					
Active or prior COVID	Excluded	N/A	Excluded	Excluded	Excluded
Fevers, cough, SOB	Excluded	Excluded if symptoms within 2 weeks unless negative COVID test	Excluded	Excluded	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	N/A
Positive COVID serology	Included	Included	N/A	Included	N/A
Analysis	Modified intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat

HCW=Healthcare workers; ICU=Intensive care unit; [1] Date when first participant was enrolled; [2] Date when final data were collected for the last participant

eTable 4. Definition of adverse events

RCT	AE definition
HERO-HCQ NCT04334148	Adverse events include general disorders and administration site conditions, psychiatric disorders, skin and subcutaneous tissue disorders, cardiac disorders, infections and infestations, nervous system disorders, gastrointestinal disorders, investigations (electrocardiogram QT prolonged and heart rate increased), ear and labyrinth disorders, renal and urinary disorders, and respiratory, thoracic and mediastinal disorders.
PATCH NCT04329923	Adverse events include abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness.
MN-COVID-PREP NCT04328467	Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and others.
Rojas-Serrano et al. NCT04318015	Examples of adverse events are as follows: abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness. Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and other.
WHIP NCT04341441	Covid-19 related symptoms, covid-19 clinical disease and medication adverse effects including gastrointestinal disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, cardiac disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, skin and subcutaneous tissue disorders, ear and labyrinth disorders, and eye disorders.

eTable 5. Baseline characteristics with additional variables and detailed information. Sample mean and standard deviation (in parenthesis) are reported for continuous variables, and the number of participants and proportion (in parenthesis) are reported for binary or categorical variables.

		HERO-HCQ NCT04334148		PATCH NCT04329923		MN-COVID-PREP NCT04328467		Rojas-Serrano et al. NCT04318015		WHIP NCT04341441	
		HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo	HCQ	Placebo	HCQ[2]	Placebo
	N (ITT)	683	676	66	66	989	494	62	65	387	191
	Age	44.2 (11.9)	43.1 (11.2)	31 (20-66)[3]	34 (23-62)[3]	41.5 (35, 49)[3]	40 (34, 48)[3]	31.0 (26.4-39)[4]	31.9 (27.2-43.7)[4]	45.7 (11.6); 44.9 (11.4)[2]	44.1 (12.7)
	Female	442 (64.7%)	446 (66.0%)	54 (82%)	37 (56%)	519 (52.5%)	241 (48.8%)	29 (42.6%)	42 (64.6%)	220 (57%)	114 (60%)
	BMI (kg/m^2)	28.3 (6.3)	28.6 (6.7)	26 (19-37)[5]	26 (20-50)[5]			26.7 (3.9)	27.2 (4.6)		
	Current smoker			0 (0%)	0 (0%)	38 (3.84%)	13 (2.6%)	20 (32.2%)[6]	23 (35.4%)[6]		
Race/ Ethnicity	White	624 (91.4%)	610 (90.2%)	55 (83%)	54 (82%)	852 (86.1%)	419 (84.8%)			334 (86%)	161 (84%)
	Asian			7 (11%)	7 (11%)	46 (4.7%)	29 (5.9%)			23 (6%)	15 (8%)
	African American	18 (2.6%)	23 (3.4%)	3 (4%)	1 (2%)	10 (1.0%)	10 (2.0%)			15 (4%)	9 (5%)
	Hispanic	39 (5.7%)	40 (5.9%)	0 (0%)	2 (3%)	40 (4.0%)	18 (3.6%)			11 (3%)	7 (4%)
Comorbidities	Asthma	58 (8.5%)	77 (11.4%)	9 (14%)	14 (21%)	91 (9.2%)	59 (11.9%)				
	Diabetes	20 (2.9%)	35 (5.2%)	1 (2%)	3 (5%)	36 (3.6%)	14 (2.8%)				
	Hypertension	99 (14.5%)	99 (14.6%)	3 (5%)	14 (21%)	145 (14.7%)	60 (12.1%)				
	None			54 (82%)	40 (61%)	646 (65.3%)	336 (68.0%)	53 (85.5%)	58 (89.2%)		
Practice Location	Emergency Department	96 (14.1%)	94 (13.9%)	38 (58%)	36 (55%)	417 (42.2%)	190 (38.5%)			48 (12%)	19 (10%)
	Internal Medicine ward			17 (26%)	18 (27%)	98 (9.9%)	56 (11.3%)			31 (8%)	20 (10%)
	ICU/anesthesia			6 (9%)	6 (9%)						
	Labor and delivery			5 (7%)	6 (9%)						
	Ambulance	66 (9.7%)	63 (9.3%)			73 (7.4%)	45 (9.1%)				
	Congregate care setting					46 (4.7%)	20 (4.0%)				
	ICU	48 (7.0%)	59 (8.7%)			184 (18.6%)	85 (17.2%)			37 (10%)	23 (12%)
	Operating room					103 (10.4%)	75 (15.2%)				
	EMS, Fire and Police First Responders									32 (8%)	16 (8%)
Occupation	Nurse	186/677 (27.5%)	167/668 (25.0%)	46 (70%)	42 (64%)						
	Physician	143/677 (21.1%)	144/668 (21.6%)	11 (17%)	16 (24%)						
	Certified Nurse Assistant			2 (3%)	2 (3%)						
	ED Technician			3 (4%)	1 (2%)						
	Respiratory therapist	15/677 (2.2%)	18/668 (2.7%)	3 (4%)	5 (7%)						
	Nurse or Physician							31 (50%)	33 (50.8%)		
	Emergency Medicine Provider					407 (41.1%)	190 (38.5%)				
	ICU provider					160 (16.2%)	83 (16.8%)				
	Anesthesia/ENT					178 (18.0%)	105 (21.3%)				
	HCW in COVID unit					76 (7.7%)	29 (5.9%)				
	Healthcare worker in congregate care setting					11 (1.1%)	4 (0.8%)				
	First responder					115 (11.6%)	65 (13.2%)				

HCQ=Hydroxychloroquine ; ITT= Intention-to-treat ; BMI=Body mass index ; ICU=Intensive care unit; ED=Emergency department ; ENT=Ear, nose, throat ; HCW=Healthcare worker

[1] HCQ group in the MN-COVID-PREP study included participants taking 400 mg once weekly or 400 mg twice weekly.

[2] HCQ group in the WHIP study included participants taking 200 mg daily or 400 mg weekly.

[3] Median (range)

[4] Median (IQR)

[5] Mean (range)

[6] Current or previous smoker

eTable 6. Results of outcome measures in each study. Sample size and the number of participants who had each outcome are reported with proportions (%) in parentheses.

	HERO-HCQ NCT04334148		PATCH NCT04329923		MN COVID-PREP NCT04328467		Rojas-Serrano et al. NCT04318015		WHIP NCT04341441	
Treatment	HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo	HCQ	Placebo	HCQ[2]	Placebo
N (ITT)	683	676	64	61	989	494	62	65	387	191
Primary Outcome										
Confirmed COVID-19	3 (0.4)	6 (0.9)	4 (6.3)	4 (6.6)	11 (1.1)	6 (1.2)	1 (1.6)	6 (9.2)	2 (0.5)	2 (1.0)
Suspected with COVID compatible symptoms	38 (5.6)	47 (7.0)			47 (4.8)	33 (6.7)			22 (5.7)	13 (6.8)
Secondary outcome										
Adverse event[3]	16 (2.3)	13 (1.9)	29 (45.3)	17 (27.9)	316 (32.0)	100 (20.2)	32 (51.6)	38 (58.5)	192 (49.6)	85 (44.5)

HCQ= Hydroxychloroquine; ITT= Intention-to-treat; AE=Adverse event ; COVID-RS=COVID-19 related symptoms ; Vit C= Vitamin C

[1] HCQ group in the MN-COVID-PREP study included participants taking 400 mg once weekly or 400 mg twice weekly.

[2] HCQ group in the WHIP study included participants taking 200 mg daily or 400 mg weekly.

[3] Number of patients with any adverse events

PRISMA 2020 Checklist

Section and Topic !	Item #	Checklist item !	Location where item is reported !
TITLE !			!
"#%&!!	'!	()&*$#+,!$-&!.&/0.$!12!1!2,2$&31$#4!.&5#&67!	'!
ABSTRACT !			!
892$.14$!!	:!	;&&!$-&!<=(;>8!:?:?!+0.!892$.14$2!4-&4@%#2$7!	A!
INTRODUCTION !			!
=1$#0*1%&!!	A!	B&24.#9&!$-&!.1$#0*1%&!+0.!$-&!.&5#&61#*!$-&!40*$&C$!0+!&C#2$#*D!@*06%&)D&7!	E!
F9%&4$#5&2!!	H!	<.05#)&!1*!&C/%#4#$!2$1$&3&*$!0+!$-&!09%&4$#5&I2J!0.!KL&2$#0*I2J!$-&!.&5#&61)).&22&27!	M!
METHODS !			!
N%#D#9#%$,!4.#$&.#1!!	E!	;/&4#+,!$-&!#*4%L2#0*!1*)!&C4%L2#0*!4.#$&.#1!+0.!$-&!.&5#&61*)!-061$L)#&2!6&.&!D.0L/&)!+0.!$-&!2,*$-&2&27!	O!
(*+0.31$#0*! 20L.4&2!!	M!	;/&4#+,!1%!)1$1912&2P!.&D#2$&.2P!6&92#$&2P!0.D1*#21$#0*2P!.&+&.&*4&!%#2$2!1*)!O$-&.!20L.4&2!2&1.4-&)!0.!40*2L%$&)!$0!#)&*$#+,!2$L)#&27!;/&4#+,!$-&!)1$&!6-&*!&14-!20L.4&!612!%12$!2&1.4-&)!0.!40*2L%$&)7!	M!
;&1.4-!2$.1$&D,!	O!	<.&2&*$!$-&!+L%!2&1.4-!2$.1$&D#&2!+0.!1%!)1$1912&2P!.&D#2$&.2!1*)!6&92#$&2P!#*4%L)#*D!1*,!+#$&.2!1*)!%#3#$2!L2&)7!	M!
;&%&4$#0*!/.04&22!	Q!	;/&4#+,!$-&!3&$-0)2!L2&)!$0!)&4#)&!6-&$-&.!1!2$L),!3&$!$-&!#*4%L2#0*!4.#$&.#1!0+!$-&!.&5#&6P!#*4%L)#*D!-061$1*,!.&5#&6&.2!24.&&*&)!&14-!.&40.)!1*)!&14-!.&/0.$!.&$.#&5&)P!6-&$-&.!$-&,!60.@&)!#*)&/&*)&*$%,P!1*)!#+!1//%#419%&P!)&$1#%2!0+!1L$031$#0*!$00%2!L2&)!#*!$-&!/.04&227!	O!
B1$1!40%&4$#0*! /.04&22!!	R!	;/&4#+,!$-&!3&$-0)2!L2&)!$0!40%&4$!)1$1!+.03!.&/0.$2P!#*4%L)#*D!-061$1*,!.&5#&6&.2!40%&4$&)!)1$1!+.03!&14-!.&/0.$P!6-&$-&.!$-&,!60.@&)!#*)&/&*)&*$%,P!1*,!/.04&22&2!+0.!09$1#*#*D!0.!40*+#.3#*D!)1$1!+.03!2$L),!#*5&2$#D1$0.2P!1*)!#+!1//%#419%&P!)&$1#%2!0+!1L$031$#0*!$00%2!L2&)!#*!$-&!/.04&227!	O!
B1$1!#$&32!!	'?1!	S#2$!1*)!)&+#*&!1%!0L$403&2!+0.!6-#4-!)1$1!6&.&!20LD-$7!;/&4#+,!6-&$-&.!1%!.&2L%$2!-1!6&.&!403/1$#9%&!6#$-!&14-!0L$403&!)031#*!#*!&14-!2$L),!6&.&!20LD-$!I&7D7!+0.!1%!3&12L.&2P!$#3&!/O#*$2P!1*1%,2&2JP!1*)!#+!*0$P!$-&!3&$-0)2!L2&)!$0!)&4#)&!6-#4-!.&2L%$2!$0!40%&4$7!	OTQ!
	'?9!	S#2$!1*)!)&+#*&!1%!0$-&.!51.#19%&2!+0.!6-#4-!)1$1!6&.&!20LD-$!I&7D7!/1.$#4/1*$!1*)!#*$&.5&*$#0*!4-1.14$&.#2$#42P!+L*)#*D!20L.4&2J7!B&24.#9&!1*,!122L3/$#0*2!31)&!190L$!1*,!3#22#*D!0.!L*4%&1.!#*+0.31$#0*7!	OTQ!
;$L),!.#2@!0+!9#12! 122&223&*$!	''!	;/&4#+,!$-&!3&$-0)2!L2&)!$0!122&22!.#2@!0+!9#12!#*!$-&!#*4%L)&)!2$L)#&2P!#*4%L)#*D!)&$1#%2!0+!$-&!$00%I2J!L2&)P!-061$1*,!.&5#&6&.2!122&22&)!&14-!2$L),!1*)!6-&$-&.!$-&,!60.@&)!#*)&/&*)&*$%,P!1*)!#+!1//%#419%&P!)&$1#%2!0+!1L$031$#0*!$00%2!L2&)!#*!$-&!/.04&227!	Q!
N++&4$!3&12L.&2!!	':!	;/&4#+,!+0.!&14-!0L$403&!$-&!&++&4$!3&12L.&I2J!I&7D7!.#2@!.1$#OP!3&1*!)#++&.&*4&J!L2&)!#*!$-&!2,*$-&2#2!0.!/.&2&*1#0*!0+!.&2L%$27!	QTR!
;,*$-&2#2! 3&$-0)2!	'A1!	B&24.#9&!$-&!/.04&22&2!L2&)!$0!)&4#)&!6-#4-!2$L)#&2!6&.&!&%D#9%&!+0.!&14-!2,*$-&2#2!I&7D7!$19L%1$#*D!$-&!2$L),!#*$&.5&*$#0*!4-1.14$&.#2$#42!1*)!403/1.#*D!1D1#*2$!$-&!/%1**&)!D.0L/2!+0.!&14-!2,*$-&2#2!I#$&3!UEJJ7!	;L//%&3&*$!
	'A9!	B&24.#9&!1*,!3&$-0)2!.&KL#.&)!$0!/.&/1.&!$-&!)1$1!+0.!/.&2&*1#0*!0.!2,*$-&2#2P!2L4-!12!-1*)%*D!0+!3#22#*D!2L331.,!2$1$#2$#42P!0.!)1$1!40*5&.2#0*27!	QTR!
	'A4!	B&24.#9&!1*,!3&$-0)2!L2&)!$0!$19L%1$&!0.!5#2L1%,!)#2/%1,!.&2L%$2!0+!#*)#5#)L1%!2$L)#&2!1*)!2,*$-&2&27!	QTR!
	'A)!	B&24.#9&!1*,!3&$-0)2!L2&)!$0!2,*$-&2#V&!.&2L%$2!1*)!/.05#)&!1!.1$#0*1%&!+0.!$-&!4-0#4&I2J7!(+!3&$1T1*1%,2#2!612!/&.+0.3&)P!)&24.#9&!$-&!30)&%I2JP!3&$-0)I2J!$0!#)&*$#+,!$-&!/.&2&*4&!1*)!&C&*$!0+!2$1$#2$#41%!-&$&.0D&*&#$,P!1*)!20+$61.&!/14@1D&I2J!L2&)7!	QTR!
	'A&!	B&24.#9&!1*,!3&$-0)2!L2&)!$0!&C/%0.&!/022#9%&!41L2&2!0+!-&$&.0D&*&#$,!1301*D!2$L),!.&2L%$2!I&7D7!2L9D.0L/!1*1%,2#2P!3&$1T.&D.&22#0*J7!	QTR!
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=&/0.$#*D!9#12! 122&223&*$!	'H!	B&24.#9&!1*,!3&$-0)2!L2&)!$0!122&22!.#2@!0+!9#12!)L&!$0!3#22#*D!.&2L%$2!#*!1!2,*$-&2#2!I1.#2#*D!+.03!.&/0.$#*D!9#12&2J7!	;L//%&3&*$!
W&.$1#*$,! 122&223&*$!	'E!	B&24.#9&!1*,!3&$-0)2!L2&)!$0!122&22!4&.$1#*$,!!0.!40*+#)&*4&J!#*!$-&!90),!0+!&5#)&*4&!+0.!1*!0L$403&7!	;L//%&3&*$!

PRISMA 2020 Checklist

Section and Topic !	Item #	Checklist item !	Location where item is reported !
RESULTS !			!
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Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomized clinical trials

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Abstract

Objective: We studied the safety and efficacy of hydroxychloroquine (HCQ) as pre-exposure prophylaxis for COVID-19 in healthcare workers (HCWs), using a meta-analysis of randomized controlled trials.

Data Sources: PubMed, and EMBASE databases were searched to identify randomized trials studying HCQ.

Study Selection: Ten randomized controlled trials (RCTs) were identified (n=5,079 participants).

Data Extraction and Synthesis: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review and meta-analysis between HCQ and placebo using a Bayesian random-effects model. A *pre-hoc* statistical analysis plan was written, and the review protocol was registered at PROSPERO (CRD42021285093)

Main Outcomes: The primary efficacy outcome was polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection and the primary safety outcome was incidence of adverse events. The secondary outcome included clinically suspected SARS-CoV-2 infection.

Results: Compared with placebo, HCWs randomized to hydroxychloroquine (HCQ) had no significant difference in PCR-confirmed SARS-CoV-2 infection (odds ratio [OR] 0.92, 95% credible interval [CI]: 0.58, 1.37) or clinically suspected SARS-CoV-2 infection (OR 0.78, 95% CI: 0.57, 1.10), and marginally significant difference in adverse events (OR 1.35, 95% CI: 1.03, 1.73).

Conclusions and Relevance: Our meta-analysis of ten RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs found that compared with placebo HCQ

does not significantly reduce the risk of confirmed or clinically suspected SARS-CoV-2 infection, while HCQ significantly increases adverse events.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This meta-analysis studied the safety and efficacy of hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers.
- Bayesian meta-analysis models with random effects fitted the data.
- The ten trials included in the meta-analysis represent wide geographical locations including US, Canada, Mexico, India, Spain, Bolivia, Venezuela, Peru, and Pakistan.
- The findings can be applied to healthcare workers but should not be generalized to a broader population.

INTRODUCTION

Early during the SARS-CoV-2 pandemic, based on *in vitro* antiviral activity of both chloroquine and hydroxychloroquine against SARS-CoV-2 [1-3], clinicians considered use of hydroxychloroquine (HCQ) for treatment and prevention of SARS-CoV-2 infection and the associated disease, COVID-19. While there are now published randomized controlled trials of HCQ for the treatment of COVID-19 in the inpatient and outpatient setting [4, 5], there remains a lack of adequately powered randomized controlled trials of HCQ for the pre-exposure prophylaxis (PrEP) of SARS-CoV-2 infection. A number of COVID-19 clinical studies including PrEP studies were planned early in the pandemic; however, several never opened to enrollment and those that did open were closed early without reaching full accrual due to the rapidly

changing landscape of preventative therapies, including vaccines, and a significant shift in public opinion of HCQ as a medical intervention for SARS-CoV-2 [6].

Vaccination access remains insufficient globally [7]. Specifically, in low-income countries only 33% of healthcare workers are fully vaccinated. While high-income countries have better coverage, overall 38% of countries did not achieve the milestone of 70% vaccination coverage for healthcare workers by the end of 2021[8]. Thus, studying the pre-exposure prophylaxis potential for a drug with a known safety profile is crucial to protect people at high risk of exposures, such as healthcare workers (HCWs) [9, 10]. Two large randomized, placebo-controlled trials testing the safety and efficacy of HCQ as pre-exposure prophylaxis for COVID-19 in HCWs [11] [12], showed potential for a modest benefit of HCQ but were both underpowered, if a modest effect exists. More trials [13-15] studying HCQ as pre-exposure prophylaxis of COVID-19 in HCWs have been published with similar limitations.

To address the most common limitation, inadequate power to show a modest effect, we conducted a formal meta-analysis of pre-exposure prophylactic HCQ studies in HCWs. We conducted a systematic search for clinical trials of pre-exposure prophylactic use of HCQ against infection of SARS-CoV-2 in HCWs, thoroughly compared similarities and differences in characteristics of the identified studies and performed a Bayesian meta-analysis to combine results of the trials.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review and meta-analysis[16]. A statistical analysis plan was written in advance and the review protocol was registered at PROSPERO (CRD42021285093).

Search strategy and information sources

We searched PubMed/Medline and Ovid/Embase databases from database inception through the final search date March 14, 2023. We used keywords related to COVID-19, HCQ, and randomized controlled trials. The full search strategies are provided in eTable 1.

Eligibility criteria and study selection

The eligibility criteria included phase II or phase III randomized controlled trials (RCTs) of hydroxychloroquine for use as pre-exposure prophylaxis in HCWs with moderate to high risk of exposure. We excluded observational studies, crossover trials, studies where the method of allocation to treatment was not truly random, duplicate studies, and non-original data studies. No language, publication date, or publication status restrictions were applied. References of prior systematic reviews and meta-analyses were also screened for related studies. Study selection involved screening of titles and abstracts followed by full-text evaluation of possible eligible studies.

Data collection process

Each of the selected studies were independently reviewed by two reviewers (AF, MH, or HH). We extracted data on the study design, baseline characteristics, interventions, and outcomes. Any disagreements of collected information between reviews were reconciled through discussion by all three reviewers.

Outcome measures

The primary efficacy outcome for the meta-analysis was laboratory confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) test and the primary safety outcome was incidence of adverse events (Table 1). The secondary efficacy outcome was suspected or probable SARS-CoV-2 infection. Included studies had the following outcome definitions: (1) laboratory confirmed SARS-CoV-2 infection defined as COVID-19 like symptoms and positive SARS-CoV-2 PCR and (2) suspected or probable SARS-CoV-2 infection defined as COVID-19 like symptoms but lack of confirmatory PCR testing.

Table 1. Treatment strategies, adherence, trial-defined primary outcome, and study duration for trials included in the meta-analysis

	Trial-defined primary outcome	Study duration	Treatment group	Randomized treatment assignment	Randomized sample size
Naggie et al.[13] (HERO-HCQ)	Confirmed (by NP swab PCR) or suspected COVID-19 infection through 30 days	60 days	HCQ	HCQ 600 mg BID loading dose for Day 1, followed by 400 mg QD for 29 days	683
			Control	Placebo	676
Abella et al.[11] (PATCH)	COVID-19 infection as determined by positive NP swab over 8 weeks	56 days (8 weeks)	HCQ	HCQ 600mg daily for 60 days	64
			Control	Placebo	61
Rajasingham et al.[12] (MN-COVID-PREP)	COVID-19 free survival time by lab confirmed or probable illness	84 days (12 weeks)	HCQ[a]	HCQ loading doses (400 mg twice 6-8hrs apart), followed by 400 mg once weekly or 400 mg twice weekly for 84 days	989
			Control	Placebo	494
Rojas-Serrano et al.[14]	Time to symptomatic respiratory infection with a positive COVID RT PCR over 60 days	60 days	HCQ	HCQ 200 mg daily for 60 days	62
			Control	Placebo	65
McKinnon et al.[15] (WHIP)	Lab confirmed cases of COVID-19 determined by either IgM and IgG serology in blood sample or RT-PCR test results Confirmed new cases of COVID-19	56 days (8 weeks)	HCQ[a]	HCQ 400 mg loading dose for Day 1, followed by 200 mg daily or 400 mg weekly on the same day of each week for 56 days	387
			Control	Placebo	191
Vijayaraghavan et al.[17]	Lab confirmed SARS-CoV-2 infection by PCR or presence of antibodies	180 days (6 months)	HCQ	HCQ 400 mg twice on the day of enrollment, followed by 400 mg once a week for a total of 12 weeks plus personal	213

			Control	protective equipment (PPE) PPE	203
Polo et al.[18] (EPICOS)	Lab confirmed symptomatic COVID-19 by PCR	84 days (12 weeks)	HCQ[b] Control	HCQ 200 mg once daily Placebo	231 223
Llanos-Cuentas et al.[19]	COVID-19 cases confirmed by PCR or serological test	28 days (4 weeks)	HCQ	HCQ loading dose of 600 mg on the first day, followed by 400 mg every other day plus PPE	36
			Control	PPE	32
Grau-Pujol et al.[20]	COVID-19 confirmed cases with seroconversion or PCR test	180 days (6 months)	HCQ	HCQ 400 mg daily for the four consecutive days, followed by 400 mg weekly	142
			Control	Placebo	127
Syed et al.[17]	COVID-19-free survival (COVID-19 confirmed by PCR)	84 days (12 weeks)	HCQ[a]	HCQ 400 mg twice for Day 1, followed by 400 weekly or HCQ 400 mg once every 3 weeks or HCQ 200 mg once every 3 weeks	154
			Control	Placebo	46

HCQ=Hydroxychloroquine

[a] More than one HCQ groups with different doses are lumped.

[b] The Polo et al. study randomized participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.

Treatment assignment

Our meta-analysis did not study HCQ dosing specific effects. For studies randomizing participants to more than one HCQ arm with different doses, all HCQ arms were merged and considered as a single HCQ arm. Such studies include the Rajasingham et al., McKinnon et al. and Syed et al. studies.

Risk of bias and certainty of evidence assessment

Two independent reviewers (AF, HH) assessed the risk of bias (low, intermediate, high) of the included studies using the Cochrane's Collaboration tool [21] (eTable 2). We assessed the certainty of evidence using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach [22].

Statistical analysis

Bayesian logistic regression meta-analysis models under two assumptions (fixed effect and random effects) were fitted to estimate the odds ratio of having an outcome between hydroxychloroquine and placebo [23]. The fixed effect model assumes that the odds ratio is constant across studies, while the random effects model accounts for heterogeneity in the odds ratios across studies. To assess and compare the goodness-of-fit of the fitted fixed and random effects models, we calculated the Watanabe-Akaike information criterion [24]. In the Bayesian models, we assigned non-informative prior distributions as no prior information was available. The odds ratios and the associated 95% credible intervals were estimated using Markov chain Monte Carlo (MCMC) algorithms. In addition, we calculated Bayesian posterior probabilities of the odds ratio smaller than 1 or 0.5 for the primary efficacy outcome, and greater than 2 for the safety outcome [25]. The standard deviation of the random effects and I^2 [26] were estimated to quantify the between-study heterogeneity, where small values of both metrics indicate slight heterogeneity. To identify publication bias, we plotted and assessed funnel plots for their symmetry, and conducted the Egger's test[27]. All Bayesian meta-analyses were conducted using the `rstan` package (version 2.21.2)[28] in R 4.0.2 [29]. We used two parallel chains, where each chain consists of 50,000 samples after a 25,000-sample burn-in. We checked convergence of the MCMC chains for all model parameters using trace plots and Gelman-Rubin diagnostic statistics [30].

Patient and public involvement

No patient involved.

RESULTS

Search results

Our database search resulted in 350 unique studies after excluding duplicates. Of those, 339 studies were screened out due to irrelevance based on title and abstract screening. Eleven studies were assessed in full-text for eligibility (Figure 1). Of those, one trial was excluded from the meta-analysis because it studied with non-healthcare worker populations. As a result, a total of ten studies in a population consisting of HCWs were identified (Table 1).

Study and patient characteristics

Study design, population, treatment strategies, and key characteristics are presented in Table 1 and eTable 3. A total of 5,079 randomized participants (2,961 randomized to HCQ) from the 10 studies were included in the meta-analysis. The ten studies defined HCWs broadly and included first responders (emergency medical services, fire, and police). The follow-up duration of the 10 studies ranged from 28 days to 180 days. The HCQ dosing scheme varied across studies, including daily dosing ranging from 200 to 600mg daily with or without a loading dose and once or twice weekly or once every three weeks dosing. The duration of therapy also varied across studies (Table 1). The trial-specific definitions of primary outcome and adverse events are comparable across trials (Table 1, eTable 4).

Baseline characteristics by randomized treatment assignment are reported (eTable 5). The average age ranged between 31 and 45. The aggregate proportion of women within each study varied across the 10 trials, with a range from 44% to 69%. In addition, the Abella et al. and Rojas-Serrano et al. studies had smaller sample size compared with the other three studies and

showed a difference in female ratio between placebo and HCQ groups. In the Naggie et al., Abella et al., Rajasingham et al., and McKinnon et al., studies, over 80% of study participants were white. The Abella et al. and Rajasingham et al. studies had high proportions of HCWs working in an emergency department (56% and 41%, respectively) and the Abella et al. study had a high proportion of nurses (67%).

Several studies reported treatment adherence assessed by two methods: self-reported adherence and/or pill count at the end of the study. The Rajasingham et al. study additionally conducted remote blood sampling to verify HCQ concentrations in a subset. Adherence varied significantly across the studies, with a low proportion of approximately 52% in the Rojas-Serrano et al. study and 97-98% in the Abella et al. study.

Results of meta-analysis

Overall, 3.4% (171/5039) developed PCR-confirmed SARS-CoV-2 infection and 5.6% (230/4087) developed suspected COVID-19 that was not laboratory confirmed. Since the goodness-of-fit assessment using Watanabe-Akaike information criterion concluded that the random effects meta-analysis model was as good as or better than the fixed effect meta-analysis model for all outcomes, we reported the results under the random effects model. Compared with placebo, HCWs randomized to HCQ had numerically lower rate of PCR-confirmed SARS-CoV-2 infection cases (odds ratio [OR] 0.92, 95% credible interval [CI]: 0.58, 1.37), and suspected or probable SARS-CoV-2 infection cases (OR 0.78, 95% CI: 0.57, 1.10). None of these odds ratios were statistically significant. Participants treated with HCQ had a numerically higher rate of adverse events (OR 1.35, 95% CI: 1.03, 1.73) with marginally statistical significance (Figure 2). The outcome data

used in our analyses are presented in eTable 6. The GRADE scores for the odds ratios with respect to all three outcomes were downgraded by 1 due to wide credible intervals of odds ratios, resulting in moderate certainty of evidence.

The Bayesian posterior probabilities of the odds ratio less than 1 for the confirmed SARS-CoV-2 infection outcome (i.e., the probability of HCQ favoring over placebo) was 0.67, while the posterior probability of odds ratio less than 0.5 (i.e., the probability that the odds of having a confirmed SARS-CoV-2 infection outcome in HCQ is less than a half of the odds in placebo) was 0.009. The posterior probability of the odds ratio greater than 2 for the adverse event outcome (i.e., the probability that the odds of having an adverse event in HCQ is greater than twice of the odds in placebo) was 0.004.

Our meta-analysis showed little or moderate variability of effect estimates across studies with I^2 value of 0%, 0%, and 43%, and the estimated standard deviation of the random effects of 0.39, 0.26, and 0.45 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection, and adverse event outcomes, respectively. Funnel plots (eFigure) showed no indication of publication bias and the associated Egger's test results supported that the funnel plots were not asymmetry with p-values of 0.308, 0.305, and 0.794 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection, and adverse event outcomes, respectively.

DISCUSSION

Understanding the pre-exposure prophylactic effect of HCQ against COVID-19 remains relevant, as its use continues, particularly in the international setting [31, 32]. Our meta-analysis

of the ten RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in 5,079 HCWs found that HCQ did not have a statistical association with fewer confirmed or suspected/probable SARS-CoV-2 infection cases compared with placebo. The geographical locations of the 10 trials included in the meta-analysis are US, Canada, Mexico, India, Spain, Bolivia, Venezuela, Peru, and Pakistan (eTable 3). While the odds ratios of most studies favor HCQ, the credible intervals remain wide suggesting low certainty in the true point estimate. Two studies including the Llanos-Cuentas et al. study conducted in Peru and the Syed et al. study conducted in Pakistan showed odds ratios favoring placebo, though the credible intervals remain wide. Furthermore, in this population, COVID-19 events rates were low, particularly for the most relevant PCR-confirmed infection outcome. The low event rate raises further concern for the uncertainty of these outcomes. Thus, if there is a minimal effect, the absolute benefit would be low. To gain more certainty, a very large study would need to be done and this is difficult to support now due to availability of highly effective vaccines. The safety profile of HCQ in the outpatient setting is well understood [33]. In these outpatient studies there was marginally statistically significant difference in adverse events in the HCQ versus the placebo arm, indicating that HCQ is less safe than placebo.

Our findings can be applied to HCWs but should not be generalized to a broader population. Our systematic search found only one published RCT of pre-exposure prophylaxis for non-healthcare worker populations and the study were excluded from our meta-analysis. This study was conducted in Singapore [34] and showed a significant reduction in the risk of COVID-19 infection in the HCQ arm when compared with the comparator arm, vitamin C. However, this study showed moderate risk of bias as it used an open-label cluster-randomization design, the

Institutional Review Board excluded higher risk persons from the hydroxychloroquine arm only, and the participants may not be representative of a general population due to the communal living environment.

A Bayesian meta-analysis approach was used to fit the data. The Bayesian meta-analysis approach has several advantages. First, its flexibility and the MCMC sampling methods to estimate posterior distributions provide probability-based quantities (e.g., posterior probability of an odds ratio smaller than 0.5) that complement typical meta-analysis results (e.g., odds ratios and the associated credible intervals) and help decision making [35]. Second, the Bayesian meta-analysis model with random effects estimates the between-study variability better than the frequentist counterparts [36]. Third, when it comes to with binary outcomes, the Bayesian approach handles rare events better than the frequentist counterparts [23].

A recently published meta-analysis by García-Albéniz et al. [37] investigated pre-exposure (seven RCTs included) and post-exposure (four RCTs included) prophylactic effects of HCQ, but not limited to the HCW population. They found significant pre-exposure prophylactic effects of HCQ on SARS-CoV-2 infection, different from ours. The seven pre-exposure prophylaxis RCTs included in the García-Albéniz et al. meta-analysis consisted of six RCTs that were in our meta-analysis and the aforementioned Singapore study that was excluded from our meta-analysis. Our meta-analysis provides the most up-to-date, systematic, and comprehensive evidence about prophylactic effects of HCQ focusing on the HCW population.

Although a meta-analysis allows for combining evidence from multiple studies in a principled way, our meta-analysis has limitations. First, our analysis did not evaluate effects of different HCQ doses and combined multiple HCQ arms using different doses in three studies. The RCTs included in our meta-analysis studied varying dosing schemes and a meta-analysis using aggregate-level data is not a sufficient source to study dosing effects. Second, detailed subgroup analyses were not conducted due to limited information. Individual-level data are required to study both dosing and subgroup effects.

Our meta-analysis of ten RCTs investigating safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs provides the most up-to-date evidence on HCQ. Although most individual trials were underpowered and showed null data, integrating the results systematically via meta-analysis contributes to the scientific literature and provides certain answers to the question. We found that HCQ does not reduce the risk of confirmed or probable SARS-CoV-2 infection, but increase risk of adverse events compared with placebo. Hydroxychloroquine should not be used for pre-exposure prophylaxis in the HCW population.

Contributors

All authors fulfill the ICMJE criteria for authorship. HH, SN, RR, and KJA designed the study. HH, AF, and MH collected and analyzed the data. HH, SN, and RR wrote the manuscript. SH and KJA provided statistical review and AF, JEM, RA, JRS, BSA, AMPV, CWW, AH and DRB provided clinical review. All authors approved and decided to submit the paper for publication.

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Competing interests

All authors except Dr. Abella reported no financial relationship with commercial interest. Dr. Abella have received NIH funds for COVID-19 related research, and holds equity in VOC Health, a start-up company that is developing novel covid testing.

Ethics Approval

Ethics approval was not required because this study used publicly available aggregate data that were not involved with patients' information or prospective data collection.

Data sharing statement

The data are presented in eTable 6.

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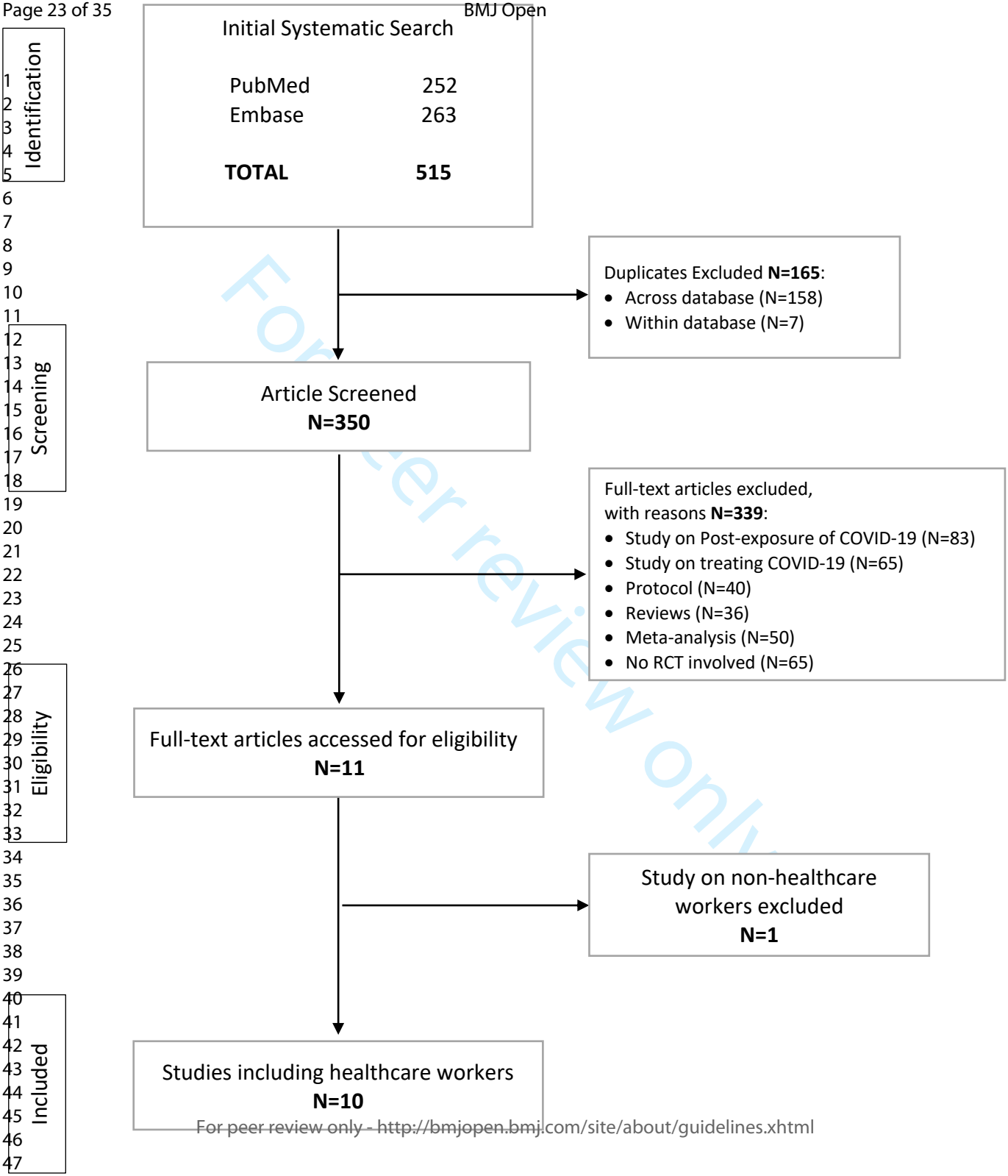
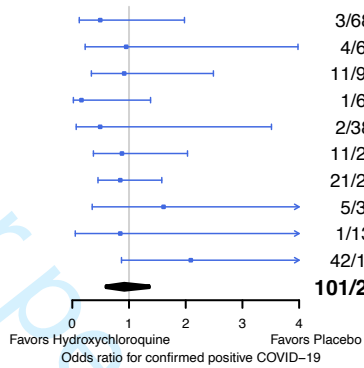
Figure Legends

Figure 1. Flowchart of literature review

Figure 2. Forest plots of the meta-analysis results showing the number of events (y), sample size (n), posterior median of odds ratios, and the associated 95% credible intervals comparing HCQ versus placebo for (a) lab-confirmed positive COVID-19, (b) suspected COVID-19, and (c) adverse events.



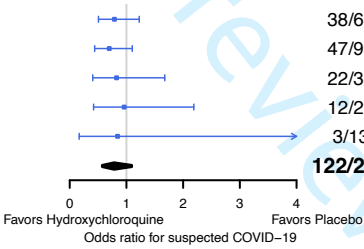
(a) Lab-confirmed positive COVID-19



Study	HCQ y/n	Placebo y/n	Odds Ratio [95%CI]
Naggie et al.	3/683	6/676	0.49 [0.12, 1.98]
Abella et al.	4/64	4/61	0.95 [0.23, 3.98]
Rajasingham et al.	11/989	6/494	0.91 [0.34, 2.49]
Rojas−Serrano et al.	1/62	6/65	0.16 [0.02, 1.38]
McKinnon et al.	2/387	2/191	0.49 [0.07, 3.51]
Vijayaraghavan et al.	11/211	12/203	0.88 [0.37, 2.03]
Polo et al.	21/224	23/211	0.85 [0.45, 1.58]
Llanos−Cuentas et al.	5/34	3/31	1.61 [0.35, 7.38]
Grau−Pujol et al.	1/137	1/116	0.85 [0.05, 13.67]
Syed et al.	42/154	7/46	2.09 [0.87, 5.03]
Meta-analysis	**101/2945**	**70/2094**	**0.92 [0.58, 1.37]**

I^2 = 0%

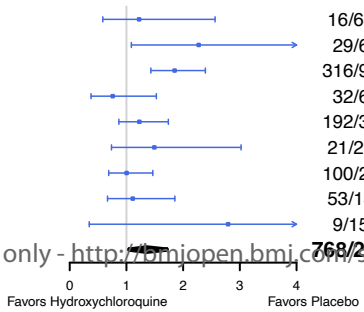
(b) Suspected COVID-19



Study	HCQ y/n	Placebo y/n	Odds Ratio [95% CI]
Naggie et al.	38/683	47/676	0.78 [0.51, 1.23]
Rajasingham et al.	47/989	33/494	0.70 [0.44, 1.10]
McKinnon et al.	22/387	13/191	0.83 [0.41, 1.68]
Vijayaraghavan et al.	12/211	12/203	0.96 [0.42, 2.19]
Grau−Pujol et al.	3/137	3/116	0.84 [0.17, 4.26]
Meta-analysis	**122/2407**	**108/1680**	**0.78 [0.57, 1.10]**

I^2 = 0%

(c) Adverse events



Study	HCQ y/n	Placebo y/n	Odds Ratio [95% CI]
Naggie et al.	16/683	13/676	1.22 [0.58, 2.56]
Abella et al.	29/65	17/65	2.27 [1.09, 4.76]
Rajasingham et al.	316/989	100/494	1.85 [1.43, 2.39]
Rojas−Serrano et al.	32/62	38/65	0.76 [0.38, 1.53]
McKinnon et al.	192/387	85/191	1.23 [0.87, 1.74]
Vijayaraghavan et al.	21/211	14/203	1.49 [0.74, 3.02]
Polo et al.	100/224	94/211	1.00 [0.69,1.47]
Grau−Pujol et al.	53/137	42/116	1.11 [0.67, 1.85]
Syed et al.	9/154	1/46	2.79 [0.34, 22.65]
Meta-analysis	**768/2912**	**404/2067**	**1.35 [1.03, 1.73]**

I^2 = 43%

Supplementary Materials

CONTENTS

eTable 1. Search code that was used to identify publications as of March 14, 2023

PubMed search

#1	covid[Title] OR coronavirus[Title] OR sars-cov-2[Title]
#2	hydroxychloroquine[Title]
#3	randomized[Title/Abstract] OR randomized[Title/Abstract]
#4	#1 AND #2 AND #3

Embase search

#1	covid:ti OR coronavirus:ti OR 'sars cov 2':ti
#2	hydroxychloroquine:ti
#3	randomized:ab,ti OR randomised:ab,ti
#4	#1 AND #2 AND #3

eTable 2. Risk of bias for trials included in the meta-analysis using the Cochrane risk assessment tool. Green circle is for low risk and yellow circle is for some concerns

	Selection bias (Randomization process)	Performance bias (Deviations from the intended interventions)	Attrition bias[1] (Missing outcome data)	Reporting bias (Measurement of the outcome)	Other sources of bias (Selection of the reported result)
Naggie et al. (HERO-HCQ)					
Abella et al. (PATCH)					
Rajasingham et al. (MN-COVID-PREP)					
Rojas-Serrano et al.					
McKinnon et al. (WHIP)					
Vijayaraghavan et al.					
Polo et al. (EPICOS)					
Llanos-Cuentas et al.					
Grau-Pujol et al.					
Syed et al.					

[1] The Rojas-Serrano et al. study reported minimal loss to follow-up (<10%). The Rojas-Serrano et al. study reported 18% (25/130) lost to follow-up and additional 12% (16/130) discontinued the intervention.

eTable 3. Characteristics of trials included in the meta-analysis

	Naggie et al. (HERO-HCQ)	Abella et al. (PATCH)	Rajasingham et al. (MN-COVID-PREP)	Rojas-Serrano et al.	McKinnon et al. (WHIP)
N (randomization)	1360	132	1496	130	624
Study start date[1]	4/22/2020	4/9/2020	4/6/2020	4/21/2020	4/10/2020
Study completion date[2]	1/9/2021	11/13/2020	7/13/2020	3/31/2021	12/14/2020
Occupation	HCWs at risk of COVID exposure through work in the ICU, emergency department, emergency services, respiratory services or COVID unit	HCWs (Physicians, nurses, certified nursing assistants, emergency technicians, respiratory therapists) eligible working >20 hrs/week	HCWs (physicians, nurses, emergency medical technicians) with direct contact with COVID patients including emergency department and ICU setting, first responders and performing aerosol generating procedures	HCWs (nurses, nursing aids, cleaning staff, orderlies, respiratory therapists and physicians) taking care of hospitalized patients with COVID	HCW, first responders and correlational/law officers, nursing home workers, medical students, public transit workers, household family members of HCW in Michigan and Ohio
Sites	34 sites across the US	2 tertiary urban hospitals	Multiple sites nationwide across US and Canada	Single site (National Institute of Respiratory Diseases of Mexico)	Multiple sites at Michigan in the US
Randomization	Yes (Phase III)	Yes (Phase II)	Yes (Phase III)	Yes (Phase III)	Yes (Phase III)
Trial type	Double-blinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	No weight requirement	<40kg excluded	<50kg excluded	N/A
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Excluded	Excluded	Excluded	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Included	Exclude
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Included	
Significant renal disease (stage IV or greater)	Excluded	Included	Excluded	Excluded	Exclude
Pregnant/breastfeeding	Included	Excluded	Included in US, Excluded in Canada	Excluded	Exclude
Medication					
Qtc prolonging medications	Excluded	Excluded	Excluded	Included	Exclude
Use of other medications with significant drug interactions	Included	Excluded	Excluded	Included	N/A
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine or azithromycin)	Any treatment for COVID-19 within 14 days excluded	Current use of HCQ or chloroquine excluded	HCQ or chloroquine within 30 days excluded	Chronic use of HCQ included
COVID-19 related criteria					
Active or prior COVID	Excluded	N/A	Excluded	Excluded	Excluded
Fevers, cough, SOB	Excluded	Excluded if symptoms within 2 weeks unless negative COVID test	Excluded	Excluded	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	N/A
Positive COVID serology	Included	Included	N/A	Included	N/A
Analysis	Modified intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat

	Vijayaraghavan et al.	Polo et al. (EPICOS)	Llanos-Cuentas et al.	Grau-Pujol et al.	Syed et al.
N (randomization)	416	454	68	269	200
Study start date[1]	6/29/2020	4/2020 Spain, 10/2020 Bolivia, 3/2021 Venezuela	June, 2020	4/4/2020	5/1/2020
Study completion date[2]	2/4/2021	5/30/2021	November, 2020	Study halted a 1 month analysis	Not reported
Occupation	HCWs in an environment with exposure to COVID-19 (physicians, nurses, allied health workers and ancillary health workers)	HCWs (physicians, nurses, medical students, other workers with and without direct patient contact)	HCWs (physicians, nursing staff, technical staff and nursing assistants involved in care of COVID-19 patients)	HCWs (physicians, nurses, nurse assistants and administrators working at least 3 days a week in the trial hospitals)	HCWs at risk of COVID-19 exposure including physicians, nurses, first responders, those performing aerosol generating procedures or working in the emergency department, ICU, and general medicine wards
Sites	9 hospitals across India	Multiple sites across Spain, Venezuela and Bolivia	4 public hospitals across the Lima metropolitan area	3 hospitals in Barcelona, Spain	Single hospital in Pakistan
Randomization	Yes	Yes	Yes (Phase III)	Yes	Yes (Phase II)
Trial type	Unblinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18-70	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	<40kg excluded	No weight requirement	No weight requirement	<40 kg
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Included	Excluded	Included	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Excluded	Excluded
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Excluded	Excluded
Significant renal disease (stage IV or greater)	Included	Excluded	Excluded	Excluded	Excluded
Pregnant/breastfeeding	Excluded	Excluded	Included	Excluded	Excluded
Medication					
Qtc prolonging medications	Excluded	Excluded	Included	Excluded	Excluded
Use of other medications with significant drug interactions	Excluded	Included	Included	Excluded	Excluded
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine azithromycin)	Any medication as prophylaxis against COVID-19 after 3/1/21	Use of hydroxychloroquine, chloroquine or azithromycin in the last 30 days excluded	Treatment with chloroquine or hydroxychloroquine within the last 1 month	Those already taking hydroxychloroquine were excluded
COVID-19 related criteria					
Active or prior COVID	Excluded	Excluded	Excluded	Excluded	Excluded
Fevers, cough, SOB	Not specified in exclusion criteria	Excluded	Not specified in exclusion criteria	Not specified in exclusion criteria	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	Excluded
Positive COVID serology	N/A	N/A	N/A	Excluded	Excluded
Analysis	Intention-to-treat	Not reported	Intention-to-treat	Intention-to-treat	Not reported

HCW=Healthcare workers; ICU=Intensive care unit; [1] Date when first participant was enrolled; [2] Date when final data were collected for the last participant

eTable 4. Definition of adverse events

Trial	AE definition
Naggie et al. (**HERO-HCQ**)	Adverse events include general disorders and administration site conditions, psychiatric disorders, skin and subcutaneous tissue disorders, cardiac disorders, infections and infestations, nervous system disorders, gastrointestinal disorders, investigations (electrocardiogram QT prolonged and heart rate increased), ear and labyrinth disorders, renal and urinary disorders, and respiratory, thoracic and mediastinal disorders.
Abella et al. (**PATCH**)	Adverse events include abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness.
Rajasingham et al. (**MN-COVID-PREP**)	Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and others.
Rojas-Serrano et al.	Examples of adverse events are as follows: abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness. Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and other.
McKinnon et al. (**WHIP**)	Covid-19 related symptoms, covid-19 clinical disease and medication adverse effects including gastrointestinal disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, cardiac disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, skin and subcutaneous tissue disorders, ear and labyrinth disorders, and eye disorders.
Vijayaraghavan et al.	Adverse events listed in each category at the participant level were categorized as cardiac, gastro-intestinal, headache, and Qtc prolongation.
Polo et al. (EPICOS)	Adverse events were classified by organ system and included: gastrointestinal disorders, blood and lymphatic system disorders, cardiac disorders, ear and labyrinth disorders, eye disorder, general disorders, immune system disorder, infections, injuries, investigations, metabolism and nutrition disorders, musculoskeletal/connective tissue disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system disorders, respiratory disorders, skin disorders and vascular disorders.
Llanos-Cuentas et al.	Adverse events from grade 1 to grade 3 and above. Note that the Llanos-Cuentas et al. study did report the number of adverse events (not participants) in the HCQ group only. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.
Grau-Pujol et al.	Adverse events included: general symptoms (fever, chills, sweating, malaise, myalgia, arthralgia), gastrointestinal symptoms (nausea, abdominal pain, diarrhea, dysgeusia), dermatological symptoms (itching, rash),respiratory symptoms (rhinorrhea, sore throat / odynophagia, cough, pleuritic pain, dyspnea), neurologic symptoms (headache, visual disturbances), and cardiovascular symptoms. Events were graded mild, moderate and severe.
Syed et al.	Syed et al. report the number of patients in each group who experienced adverse events, but did not report what the events were. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.

eTable 5. Baseline characteristics with additional variables and detailed information. Sample mean and standard deviation (in parenthesis) are reported for continuous variables, and the number of participants and proportion (in parenthesis) are reported for binary or categorical variables.

		Naggie et al. (HERO-HCQ)		Abella et al. (PATCH)		Rajasingham et al. (MN-COVID-PREP)		Rojas-Serrano et al.		McKinnon et al. (WHIP)	
		HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo	HCQ	Placebo	HCQ[1]	Placebo
	N (randomization)	683	676	66	66	989	494	62	65	387	191
	Age	44.2 (11.9)	43.1 (11.2)	31 (20-66)[3]	34 (23-62)[3]	41.5 (35, 49)[3]	40 (34, 48)[3]	31.0 (26.4-39)[4]	31.9 (27.2-43.7)[4]	45.7 (11.6); 44.9 (11.4)[2]	44.1 (12.7)
	Female	442 (64.7%)	446 (66.0%)	54 (82%)	37 (56%)	519 (52.5%)	241 (48.8%)	29 (42.6%)	42 (64.6%)	220 (57%)	114 (60%)
	BMI (kg/m^2)	28.3 (6.3)	28.6 (6.7)	26 (19-37)[5]	26 (20-50)[5]			26.7 (3.9)	27.2 (4.6)		
	Current smoker			0 (0%)	0 (0%)	38 (3.84%)	13 (2.6%)	20 (32.2%)[6]	23 (35.4%)[6]		
Race/ Ethnicity	White	624 (91.4%)	610 (90.2%)	55 (83%)	54 (82%)	852 (86.1%)	419 (84.8%)			334 (86%)	161 (84%)
	Asian			7 (11%)	7 (11%)	46 (4.7%)	29 (5.9%)			23 (6%)	15 (8%)
	African American	18 (2.6%)	23 (3.4%)	3 (4%)	1 (2%)	10 (1.0%)	10 (2.0%)			15 (4%)	9 (5%)
	Hispanic	39 (5.7%)	40 (5.9%)	0 (0%)	2 (3%)	40 (4.0%)	18 (3.6%)			11 (3%)	7 (4%)
Comorbidities	Asthma	58 (8.5%)	77 (11.4%)	9 (14%)	14 (21%)	91 (9.2%)	59 (11.9%)				
	Diabetes	20 (2.9%)	35 (5.2%)	1 (2%)	3 (5%)	36 (3.6%)	14 (2.8%)				
	Hypertension	99 (14.5%)	99 (14.6%)	3 (5%)	14 (21%)	145 (14.7%)	60 (12.1%)				
	None			54 (82%)	40 (61%)	646 (65.3%)	336 (68.0%)	53 (85.5%)	58 (89.2%)		
Practice Location	Emergency Department	96 (14.1%)	94 (13.9%)	38 (58%)	36 (55%)	417 (42.2%)	190 (38.5%)			48 (12%)	19 (10%)
	Internal Medicine ward			17 (26%)	18 (27%)	98 (9.9%)	56 (11.3%)			31 (8%)	20 (10%)
	ICU/anesthesia			6 (9%)	6 (9%)						
	Labor and delivery			5 (7%)	6 (9%)						
	Ambulance	66 (9.7%)	63 (9.3%)			73 (7.4%)	45 (9.1%)				
	Congregate care setting					46 (4.7%)	20 (4.0%)				
	ICU	48 (7.0%)	59 (8.7%)			184 (18.6%)	85 (17.2%)			37 (10%)	23 (12%)
	Operating room					103 (10.4%)	75 (15.2%)				
	EMS, Fire and Police First Responders									32 (8%)	16 (8%)
Occupation	Nurse	186/677 (27.5%)	167/668 (25.0%)	46 (70%)	42 (64%)						
	Physician	143/677 (21.1%)	144/668 (21.6%)	11 (17%)	16 (24%)						
	Certified Nurse Assistant			2 (3%)	2 (3%)						
	ED Technician			3 (4%)	1 (2%)						
	Respiratory therapist	15/677 (2.2%)	18/668 (2.7%)	3 (4%)	5 (7%)						
	Nurse or Physician							31 (50%)	33 (50.8%)		
	Emergency Medicine Provider					407 (41.1%)	190 (38.5%)				
	ICU provider					160 (16.2%)	83 (16.8%)				
	Anesthesia/ENT					178 (18.0%)	105 (21.3%)				
	HCW in COVID unit					76 (7.7%)	29 (5.9%)				
	Healthcare worker in congregate care setting					11 (1.1%)	4 (0.8%)				
	First responder					115 (11.6%)	65 (13.2%)				

		Vijayaraghavan et al.		Polo et al. (EPICOS)		Llanos-Cuentas et al.		Grau-Pujol et al.		Syed et al.	
		HCQ	Placebo	HCQ[2]	Placebo	HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo
	N (randomization)	213	203	231	223	36	32	142	127	154	46
	Age	32.3 (9.65)	31.8 (8.63)	38 (18-65)	38 (18,65)	39.14 (1.53)	39.28 (1.72)	39.6 (11.2)	40.3 (12.8)	30.25 (NA)	31.9 (9.13)
	Female	100 (46.9%)	97 (47.8%)	149 (64.5%)	143 (64.1%)	20 (55.6%)	20 (62.5%)	104 (73.2%)	93 (73.2%)	68 (44.1%)	23 (50%)
	BMI (kg/m^2)										
	Current smoker	8 (3.8%)	9 (4.4%)					21 (14.9%)	17 (13.8%)	19 (12.3%)	7 (15.2%)
Race/ Ethnicity	White										
	Asian										
	African American										
	Hispanic										
Comorbidities	Asthma	0 (0%)	0 (0%)	20 (8.7%)	9 (4.0%)	3 (8.3%)	4 (12.5%)	5 (3.5%)	2 (1.6%)		
	Diabetes	7 (3.3%)	3 (1.5%)	1 (0.4%)	3 (1.3%)	1 (2.8%)	0 (0%)	0 (0%)	1 (0.8%)	4 (2.6%)	3 (6.5%)
	Hypertension	2 (0.9%)	3 (1.5%)	4 (1.7%)	19 (8.5%)	3 (8.3%)	2 (6.3%)	2 (1.4%)	3 (2.4%)	7 (4.5%)	2 (4.3%)
	None										
Practice Location	Emergency Department	26 (12.2%)	18 (8.9%)	20 (8.7%)	21 (9.4%)						
	Internal Medicine ward	130 (64%)	130 (61%)								
	ICU/anesthesia										
	Labor and delivery										
	Ambulance			0 (0%)	0 (0%)						
	Congregate care setting										
	ICU	53 (24.9%)	53 (26.1%)	17 (7.4%)	13 (5.8%)						
	Operating room										
	EMS, Fire and Police First Responders										
Occupation	Nurse	67 (31.5%)	68 (33.5%)	67 (29.0%)	72 (32.3%)	6 (16.7%)	5 (15.6%)	35 (27.8%)	40 (28.2%)	20 (13.0%)	9 (19.6%)
	Physician	34 (16%)	31 (15.3%)	74 (32%)	66 (29.6%)	23 (63.9%)	16 (50%)	67 (47.2%)	53 (42.1%)	118 (76.6%)	25 (54.3%)
	Certified Nurse Assistant					1 (2.8%)	0 (0%)	12 (8.5%)	12 (9.5%)		
	ED Technician										
	Respiratory therapist										
	Nurse or Physician										
	Emergency Medicine Provider									2 (1.3%)	0 (0%)
	ICU provider										
	Anesthesia/ENT										
	HCW in COVID unit										
	Healthcare worker in congregate care setting										
	First responder									2 (1.3%)	0 (0%)

HCQ=Hydroxychloroquine ; ITT= Intention-to-treat ; BMI=Body mass index ; ICU=Intensive care unit; ED=Emergency department ; ENT=Ear, nose, throat ; HCW=Healthcare worker

[1] More than one HCQ groups with different doses are lumped.

[2] The Polo et al. study randomized participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.

[3] Median (range)

[4] Median (IQR)

[5] Mean (range)

[6] Current or previous smoker

eTable 6. Results of outcome measures in trials included in the meta-analysis. Sample size and the number of participants who had each outcome are reported with proportions (%) in parentheses.

	Treatment	N (ITT)	Confirmed COVID-19	Suspected with COVID compatible symptoms	Adverse event[2]
Naggie et al. (HERO-HCQ)	HCQ	683	3 (0.4)	38 (5.6)	16 (2.3)
	Placebo	676	6 (0.9)	47 (7.0)	13 (1.9)
Abella et al. (PATCH)	HCQ	64	4 (6.3)		29 (45.3)
	Placebo	61	4 (6.6)		17 (27.9)
Rajasingham et al. (MN-COVID-PREP)	HCQ[1]	989	11 (1.1)	47 (4.8)	316 (32.0)
	Placebo	494	6 (1.2)	33 (6.7)	100 (20.2)
Rojas-Serrano et al.	HCQ	62	1 (1.6)		32 (51.6)
	Placebo	65	6 (9.2)		38 (58.5)
McKinnon et al. (WHIP)	HCQ[1]	387	2 (0.5)	22 (5.7)	192 (49.6)
	Placebo	191	2 (1.0)	13 (6.8)	85 (44.5)
Vijayaraghavan et al.	HCQ	211	11 (5.2)	12 (5.7)	21 (10.0)
	Placebo	203	12 (5.9)	12 (5.9)	14 (6.9)
Polo et al. (EPICOS)	HCQ	224	21 (9.4)		100 (44.6)
	Placebo	211	23 (10.9)		94 (44.5)
Llanos-Cuentas et al.	HCQ	34	5 (14.7)		
	Placebo	31	3 (9.7)		
Grau-Pujol et al.	HCQ	137	1 (0.7)	3 (2.2)	53 (38.7)
	Placebo	116	1 (0.9)	3 (2.6)	42 (36.2)
Syed et al.	HCQ[1]	154	42 (27.3)		9 (5.8)
	Placebo	46	7 (15.2)		1 (2.2)

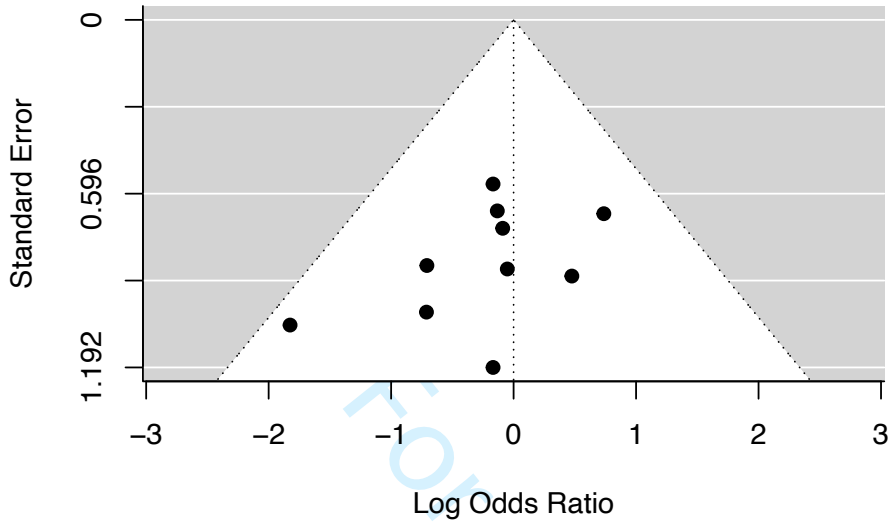
HCQ= Hydroxychloroquine; ITT= Intention-to-treat; AE=Adverse event ; COVID-RS=COVID-19 related symptoms ; Vit C= Vitamin C

[1] More than one HCQ groups with different doses are lumped.

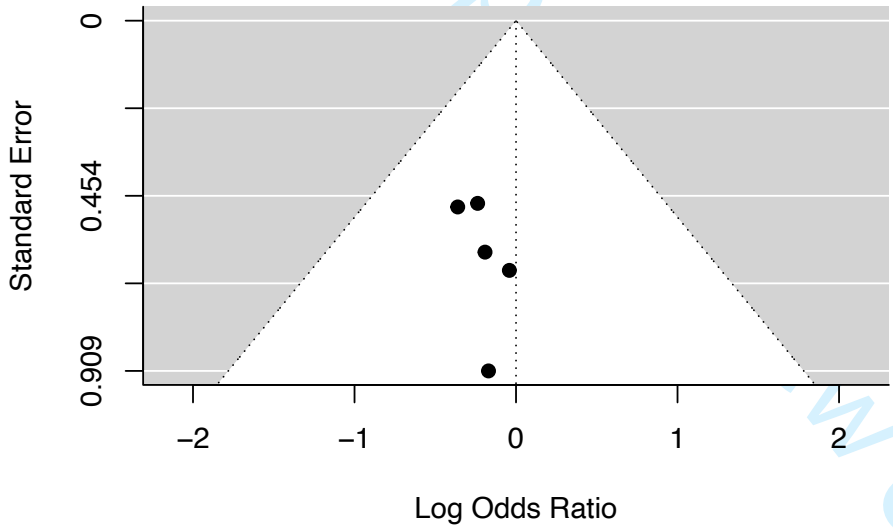
[2] Number of patients with any adverse events

eFigure. Funnel plots for the three outcomes

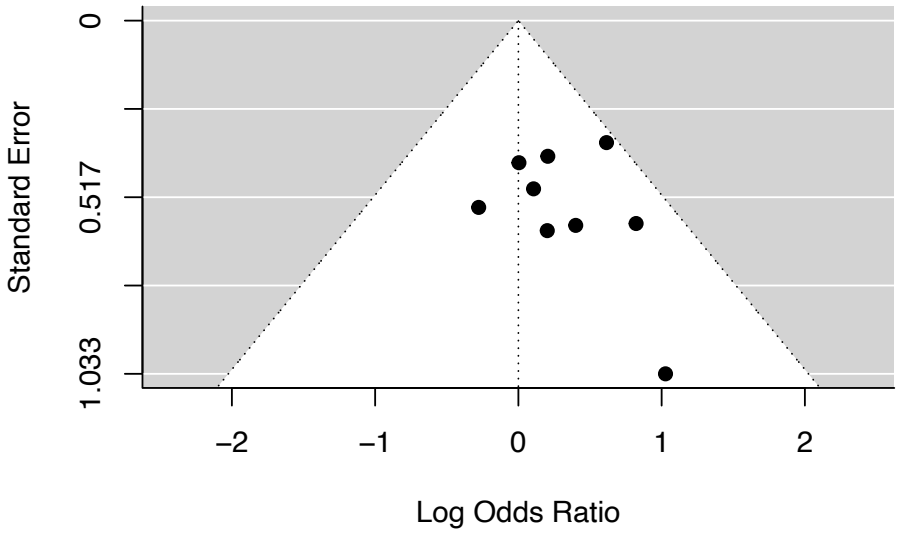
(a) Lab-confirmed positive COVID-19



(b) Suspected COVID-19



(c) Adverse events



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Supplement
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	11-12
Study characteristics	17	Cite each included study and present its characteristics.	8-9, Supplement
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplement
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplement
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11-13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplement
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplement
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14
	23b	Discuss any limitations of the evidence included in the review.	16
	23c	Discuss any limitations of the review processes used.	16
	23d	Discuss implications of the results for practice, policy, and future research.	16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Supplement
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplement

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomized clinical trials

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Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomized clinical trials

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Abstract

Objective: We studied the safety and efficacy of hydroxychloroquine (HCQ) as pre-exposure prophylaxis for COVID-19 in healthcare workers (HCWs), using a meta-analysis of randomized controlled trials.

Data Sources: PubMed, and EMBASE databases were searched to identify randomized trials studying HCQ.

Study Selection: Ten randomized controlled trials (RCTs) were identified (n=5,079 participants).

Data Extraction and Synthesis: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review and meta-analysis between HCQ and placebo using a Bayesian random-effects model. A *pre-hoc* statistical analysis plan was written, and the review protocol was registered at PROSPERO (CRD42021285093)

Main Outcomes: The primary efficacy outcome was polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection and the primary safety outcome was incidence of adverse events. The secondary outcome included clinically suspected SARS-CoV-2 infection.

Results: Compared with placebo, HCWs randomized to hydroxychloroquine (HCQ) had no significant difference in PCR-confirmed SARS-CoV-2 infection (odds ratio [OR] 0.92, 95% credible interval [CI]: 0.58, 1.37) or clinically suspected SARS-CoV-2 infection (OR 0.78, 95% CI: 0.57, 1.10), and marginally significant difference in adverse events (OR 1.35, 95% CI: 1.03, 1.73).

Conclusions and Relevance: Our meta-analysis of ten RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs found that compared with placebo HCQ

does not significantly reduce the risk of confirmed or clinically suspected SARS-CoV-2 infection, while HCQ significantly increases adverse events.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Bayesian meta-analysis models with random effects fitted the data.
- The ten trials included in the meta-analysis represent wide geographical locations including US, Canada, Mexico, India, Spain, Bolivia, Venezuela, Peru, and Pakistan.
- The findings can be applied to healthcare workers but should not be generalized to a broader population.

INTRODUCTION

Early during the SARS-CoV-2 pandemic, based on *in vitro* antiviral activity of both chloroquine and hydroxychloroquine against SARS-CoV-2 [1-3], clinicians considered use of hydroxychloroquine (HCQ) for treatment and prevention of SARS-CoV-2 infection and the associated disease, COVID-19. While there are now published randomized controlled trials of HCQ for the treatment of COVID-19 in the inpatient and outpatient setting [4, 5], there remains a lack of adequately powered randomized controlled trials of HCQ for the pre-exposure prophylaxis (PrEP) of SARS-CoV-2 infection. A number of COVID-19 clinical studies including PrEP studies were planned early in the pandemic; however, several never opened to enrollment and those that did open were closed early without reaching full accrual due to the rapidly changing landscape of preventative therapies, including vaccines, and a significant shift in public opinion of HCQ as a medical intervention for SARS-CoV-2 [6].

Vaccination access remains insufficient globally [7]. Specifically, in low-income countries only 33% of healthcare workers are fully vaccinated. While high-income countries have better coverage, overall 38% of countries did not achieve the milestone of 70% vaccination coverage for healthcare workers by the end of 2021[8]. Thus, studying the pre-exposure prophylaxis potential for a drug with a known safety profile is crucial to protect people at high risk of exposures, such as healthcare workers (HCWs) [9, 10]. Two large randomized, placebo-controlled trials testing the safety and efficacy of HCQ as pre-exposure prophylaxis for COVID-19 in HCWs [11] [12], showed potential for a modest benefit of HCQ but were both underpowered, if a modest effect exists. More trials [13-15] studying HCQ as pre-exposure prophylaxis of COVID-19 in HCWs have been published with similar limitations.

To address the most common limitation, inadequate power to show a modest effect, we conducted a formal meta-analysis of pre-exposure prophylactic HCQ studies in HCWs. We conducted a systematic search for clinical trials of pre-exposure prophylactic use of HCQ against infection of SARS-CoV-2 in HCWs, thoroughly compared similarities and differences in characteristics of the identified studies and performed a Bayesian meta-analysis to combine results of the trials.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review and meta-analysis[16]. A statistical analysis plan was written in advance and the review protocol was registered at PROSPERO (CRD42021285093).

Search strategy and information sources

We searched PubMed/Medline and Ovid/Embase databases from database inception through the final search date March 14, 2023. We used keywords related to COVID-19, HCQ, and randomized controlled trials. The full search strategies are provided in eTable 1.

Eligibility criteria and study selection

The eligibility criteria included phase II or phase III randomized controlled trials (RCTs) of hydroxychloroquine for use as pre-exposure prophylaxis in HCWs with moderate to high risk of exposure. We excluded observational studies, crossover trials, studies where the method of allocation to treatment was not truly random, duplicate studies, and non-original data studies. No language, publication date, or publication status restrictions were applied. References of prior systematic reviews and meta-analyses were also screened for related studies. Study selection involved screening of titles and abstracts followed by full-text evaluation of possible eligible studies.

Data collection process

Each of the selected studies were independently reviewed by two reviewers (AF, MH, or HH). We extracted data on the study design, baseline characteristics, interventions, and outcomes. Any disagreements of collected information between reviews were reconciled through discussion by all three reviewers.

Outcome measures

The primary efficacy outcome for the meta-analysis was laboratory confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) test and the primary safety outcome was incidence

of adverse events (Table 1). The secondary efficacy outcome was suspected or probable SARS-CoV-2 infection. Included studies had the following outcome definitions: (1) laboratory confirmed SARS-CoV-2 infection defined as COVID-19 like symptoms and positive SARS-CoV-2 PCR and (2) suspected or probable SARS-CoV-2 infection defined as COVID-19 like symptoms but lack of confirmatory PCR testing.

Table 1. Treatment strategies, adherence, trial-defined primary outcome, and study duration for trials included in the meta-analysis

	Trial-defined primary outcome	Study duration	Treatment group	Randomized treatment assignment	Randomized sample size
Naggie et al.[13] (HERO-HCQ)	Confirmed (by NP swab PCR) or suspected COVID-19 infection through 30 days	60 days	HCQ	HCQ 600 mg BID loading dose for Day 1, followed by 400 mg QD for 29 days	683
			Control	Placebo	676
Abella et al.[11] (PATCH)	COVID-19 infection as determined by positive NP swab over 8 weeks	56 days (8 weeks)	HCQ	HCQ 600mg daily for 60 days	64
			Control	Placebo	61
Rajasingham et al.[12] (MN-COVID-PREP)	COVID-19 free survival time by lab confirmed or probable illness	84 days (12 weeks)	HCQ[a]	HCQ loading doses (400 mg twice 6-8hrs apart), followed by 400 mg once weekly or 400 mg twice weekly for 84 days	989
			Control	Placebo	494
Rojas-Serrano et al.[14]	Time to symptomatic respiratory infection with a positive COVID RT PCR over 60 days	60 days	HCQ	HCQ 200 mg daily for 60 days	62
			Control	Placebo	65
McKinnon et al.[15] (WHIP)	Lab confirmed cases of COVID-19 determined by either IgM and IgG serology in blood sample or RT-PCR test results Confirmed new cases of COVID-19	56 days (8 weeks)	HCQ[a]	HCQ 400 mg loading dose for Day 1, followed by 200 mg daily or 400 mg weekly on the same day of each week for 56 days	387
			Control	Placebo	191
Vijayaraghavan et al.[17]	Lab confirmed SARS-CoV-2 infection by PCR or presence of antibodies	180 days (6 months)	HCQ	HCQ 400 mg twice on the day of enrollment, followed by 400 mg once a week for a total of 12 weeks plus personal protective equipment (PPE)	213
			Control	PPE	203
Polo et al.[18] (EPICOS)	Lab confirmed symptomatic COVID-19 by PCR	84 days (12 weeks)	HCQ[b]	HCQ 200 mg once daily	231
			Control	Placebo	223

Llanos-Cuentas et al.[19]	COVID-19 cases confirmed by PCR or serological test	28 days (4 weeks)	HCQ	HCQ loading dose of 600 mg on the first day, followed by 400 mg every other day plus PPE	36
			Control	PPE	32
Grau-Pujol et al.[20]	COVID-19 confirmed cases with seroconversion or PCR test	180 days (6 months)	HCQ	HCQ 400 mg daily for the four consecutive days, followed by 400 mg weekly	142
			Control	Placebo	127
Syed et al.[17]	COVID-19-free survival (COVID-19 confirmed by PCR)	84 days (12 weeks)	HCQ[a]	HCQ 400 mg twice for Day 1, followed by 400 weekly or HCQ 400 mg once every 3 weeks or HCQ 200 mg once every 3 weeks	154
			Control	Placebo	46

HCQ=Hydroxychloroquine

[a] More than one HCQ groups with different doses are lumped.

[b] The Polo et al. study randomized participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.

Treatment assignment

Our meta-analysis did not study HCQ dosing specific effects. For studies randomizing participants to more than one HCQ arm with different doses, all HCQ arms were merged and considered as a single HCQ arm. Such studies include the Rajasingham et al., McKinnon et al. and Syed et al. studies.

Risk of bias and certainty of evidence assessment

Two independent reviewers (AF, HH) assessed the risk of bias (low, intermediate, high) of the included studies using the Cochrane's Collaboration tool [21] (eTable 2). We assessed the certainty of evidence using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach [22].

Statistical analysis

Bayesian logistic regression meta-analysis models under two assumptions (fixed effect and random effects) were fitted to estimate the odds ratio of having an outcome between hydroxychloroquine and placebo [23]. The fixed effect model assumes that the odds ratio is constant across studies, while the random effects model accounts for heterogeneity in the odds ratios across studies. To assess and compare the goodness-of-fit of the fitted fixed and random effects models, we calculated the Watanabe-Akaike information criterion [24]. In the Bayesian models, we assigned non-informative prior distributions as no prior information was available. The odds ratios and the associated 95% credible intervals were estimated using Markov chain Monte Carlo (MCMC) algorithms. In addition, we calculated Bayesian posterior probabilities of the odds ratio smaller than 1 or 0.5 for the primary efficacy outcome, and greater than 2 for the safety outcome [25]. The standard deviation of the random effects and I^2 [26] were estimated to quantify the between-study heterogeneity, where small values of both metrics indicate slight heterogeneity. To identify publication bias, we plotted and assessed funnel plots for their symmetry, and conducted the Egger's test[27]. All Bayesian meta-analyses were conducted using the `rstan` package (version 2.21.2)[28] in R 4.0.2 [29]. We used two parallel chains, where each chain consists of 50,000 samples after a 25,000-sample burn-in. We checked convergence of the MCMC chains for all model parameters using trace plots and Gelman-Rubin diagnostic statistics [30].

Patient and public involvement

No patient involved.

RESULTS

Search results

Our database search resulted in 350 unique studies after excluding duplicates. Of those, 339 studies were screened out due to irrelevance based on title and abstract screening. Eleven studies were assessed in full-text for eligibility (Figure 1). Of those, one trial was excluded from the meta-analysis because it studied with non-healthcare worker populations. As a result, a total of ten studies in a population consisting of HCWs were identified (Table 1).

Study and patient characteristics

Study design, population, treatment strategies, and key characteristics are presented in Table 1 and eTable 3. A total of 5,079 randomized participants (2,961 randomized to HCQ) from the 10 studies were included in the meta-analysis. The ten studies defined HCWs broadly and included first responders (emergency medical services, fire, and police). The follow-up duration of the 10 studies ranged from 28 days to 180 days. The HCQ dosing scheme varied across studies, including daily dosing ranging from 200 to 600mg daily with or without a loading dose and once or twice weekly or once every three weeks dosing. The duration of therapy also varied across studies (Table 1). The trial-specific definitions of primary outcome and adverse events are comparable across trials (Table 1, eTable 4).

Baseline characteristics by randomized treatment assignment are reported (eTable 5). The average age ranged between 31 and 45. The aggregate proportion of women within each study varied across the 10 trials, with a range from 44% to 69%. In addition, the Abella et al. and Rojas-Serrano et al. studies had smaller sample size compared with the other three studies and showed a difference in female ratio between placebo and HCQ groups. In the Naggie et al.,

Abella et al., Rajasingham et al., and McKinnon et al., studies, over 80% of study participants were white. The Abella et al. and Rajasingham et al. studies had high proportions of HCWs working in an emergency department (56% and 41%, respectively) and the Abella et al. study had a high proportion of nurses (67%).

Several studies reported treatment adherence assessed by two methods: self-reported adherence and/or pill count at the end of the study. The Rajasingham et al. study additionally conducted remote blood sampling to verify HCQ concentrations in a subset. Adherence varied significantly across the studies, with a low proportion of approximately 52% in the Rojas-Serrano et al. study and 97-98% in the Abella et al. study.

Results of meta-analysis

Overall, 3.4% (171/5039) developed PCR-confirmed SARS-CoV-2 infection and 5.6% (230/4087) developed suspected COVID-19 that was not laboratory confirmed. Since the goodness-of-fit assessment using Watanabe-Akaike information criterion concluded that the random effects meta-analysis model was as good as or better than the fixed effect meta-analysis model for all outcomes, we reported the results under the random effects model. Compared with placebo, HCWs randomized to HCQ had numerically lower rate of PCR-confirmed SARS-CoV-2 infection cases (odds ratio [OR] 0.92, 95% credible interval [CI]: 0.58, 1.37; GRADE score: moderate certainty), and suspected or probable SARS-CoV-2 infection cases (OR 0.78, 95% CI: 0.57, 1.10; GRADE score: moderate certainty). None of these odds ratios were statistically significant. Participants treated with HCQ had a numerically higher rate of adverse events (OR 1.35, 95% CI: 1.03, 1.73; GRADE score: moderate certainty) with marginally statistical significance (Figure 2). The

outcome data used in our analyses are presented in eTable 6. The summary of GRADE score assessment is provided in eTable 7.

The Bayesian posterior probabilities of the odds ratio less than 1 for the confirmed SARS-CoV-2 infection outcome (i.e., the probability of HCQ favoring over placebo) was 0.67, while the posterior probability of odds ratio less than 0.5 (i.e., the probability that the odds of having a confirmed SARS-CoV-2 infection outcome in HCQ is less than a half of the odds in placebo) was 0.009. The posterior probability of the odds ratio greater than 2 for the adverse event outcome (i.e., the probability that the odds of having an adverse event in HCQ is greater than twice of the odds in placebo) was 0.004.

Our meta-analysis showed little or moderate variability of effect estimates across studies with I^2 value of 0%, 0%, and 43%, and the estimated standard deviation of the random effects of 0.39, 0.26, and 0.45 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection, and adverse event outcomes, respectively. Funnel plots (eFigure) showed no indication of publication bias and the associated Egger's test results supported that the funnel plots were not asymmetry with p-values of 0.308, 0.305, and 0.794 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection, and adverse event outcomes, respectively.

DISCUSSION

Understanding the pre-exposure prophylactic effect of HCQ against COVID-19 remains relevant, as its use continues, particularly in the international setting [31, 32]. Our meta-analysis of the ten RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in

5,079 HCWs found that HCQ did not have a statistical association with fewer confirmed or suspected/probable SARS-CoV-2 infection cases compared with placebo. The geographical locations of the 10 trials included in the meta-analysis are US, Canada, Mexico, India, Spain, Bolivia, Venezuela, Peru, and Pakistan (eTable 3). While the odds ratios of most studies favor HCQ, the credible intervals remain wide suggesting low certainty in the true point estimate. Two studies including the Llanos-Cuentas et al. study conducted in Peru and the Syed et al. study conducted in Pakistan showed odds ratios favoring placebo, though the credible intervals remain wide. Furthermore, in this population, COVID-19 events rates were low, particularly for the most relevant PCR-confirmed infection outcome. The low event rate raises further concern for the uncertainty of these outcomes. Thus, if there is a minimal effect, the absolute benefit would be low. To gain more certainty, a very large study would need to be done and this is difficult to support now due to availability of highly effective vaccines. The safety profile of HCQ in the outpatient setting is well understood [33]. In these outpatient studies there was marginally statistically significant difference in adverse events in the HCQ versus the placebo arm, indicating that HCQ is less safe than placebo.

Our findings can be applied to HCWs but should not be generalized to a broader population. Our systematic search found only one published RCT of pre-exposure prophylaxis for non-healthcare worker populations and the study were excluded from our meta-analysis. This study was conducted in Singapore [34] and showed a significant reduction in the risk of COVID-19 infection in the HCQ arm when compared with the comparator arm, vitamin C. However, this study showed moderate risk of bias as it used an open-label cluster-randomization design, the Institutional Review Board excluded higher risk persons from the hydroxychloroquine arm only,

and the participants may not be representative of a general population due to the communal living environment.

A Bayesian meta-analysis approach was used to fit the data. The Bayesian meta-analysis approach has several advantages. First, its flexibility and the MCMC sampling methods to estimate posterior distributions provide probability-based quantities (e.g., posterior probability of an odds ratio smaller than 0.5) that complement typical meta-analysis results (e.g., odds ratios and the associated credible intervals) and help decision making [35]. Second, the Bayesian meta-analysis model with random effects estimates the between-study variability better than the frequentist counterparts [36]. Third, when it comes to with binary outcomes, the Bayesian approach handles rare events better than the frequentist counterparts [23].

A recently published meta-analysis by García-Albéniz et al. [37] investigated pre-exposure (seven RCTs included) and post-exposure (four RCTs included) prophylactic effects of HCQ, but not limited to the HCW population. They found significant pre-exposure prophylactic effects of HCQ on SARS-CoV-2 infection, different from ours. The seven pre-exposure prophylaxis RCTs included in the García-Albéniz et al. meta-analysis consisted of six RCTs that were in our meta-analysis and the aforementioned Singapore study that was excluded from our meta-analysis. Our meta-analysis provides the most up-to-date, systematic, and comprehensive evidence about prophylactic effects of HCQ focusing on the HCW population.

Although a meta-analysis allows for combining evidence from multiple studies in a principled way, our meta-analysis has limitations. First, our analysis did not evaluate effects of different

HCQ doses and combined multiple HCQ arms using different doses in three studies. The RCTs included in our meta-analysis studied varying dosing schemes and a meta-analysis using aggregate-level data is not a sufficient source to study dosing effects. Second, detailed subgroup analyses were not conducted due to limited information. Individual-level data are required to study both dosing and subgroup effects.

Our meta-analysis of ten RCTs investigating safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs provides the most up-to-date evidence on HCQ. Although most individual trials were underpowered and showed null data, integrating the results systematically via meta-analysis contributes to the scientific literature and provides certain answers to the question. We found that HCQ does not reduce the risk of confirmed or probable SARS-CoV-2 infection, but increase risk of adverse events compared with placebo. Hydroxychloroquine should not be used for pre-exposure prophylaxis in the HCW population.

Contributors

All authors fulfill the ICMJE criteria for authorship. HH, SN, RR, and KJA designed the study. HH, AF, and MH collected and analyzed the data. HH, SN, and RR wrote the manuscript. SH and KJA provided statistical review and AF, JEM, RA, JRS, BSA, AMPV, CWW, AH and DRB provided clinical review. All authors approved and decided to submit the paper for publication.

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Competing interests

All authors except Dr. Abella reported no financial relationship with commercial interest. Dr. Abella have received NIH funds for COVID-19 related research, and holds equity in VOC Health, a start-up company that is developing novel covid testing.

Ethics Approval

Ethics approval was not required because this study used publicly available aggregate data that were not involved with patients' information or prospective data collection.

Data sharing statement

The data are presented in eTable 6.

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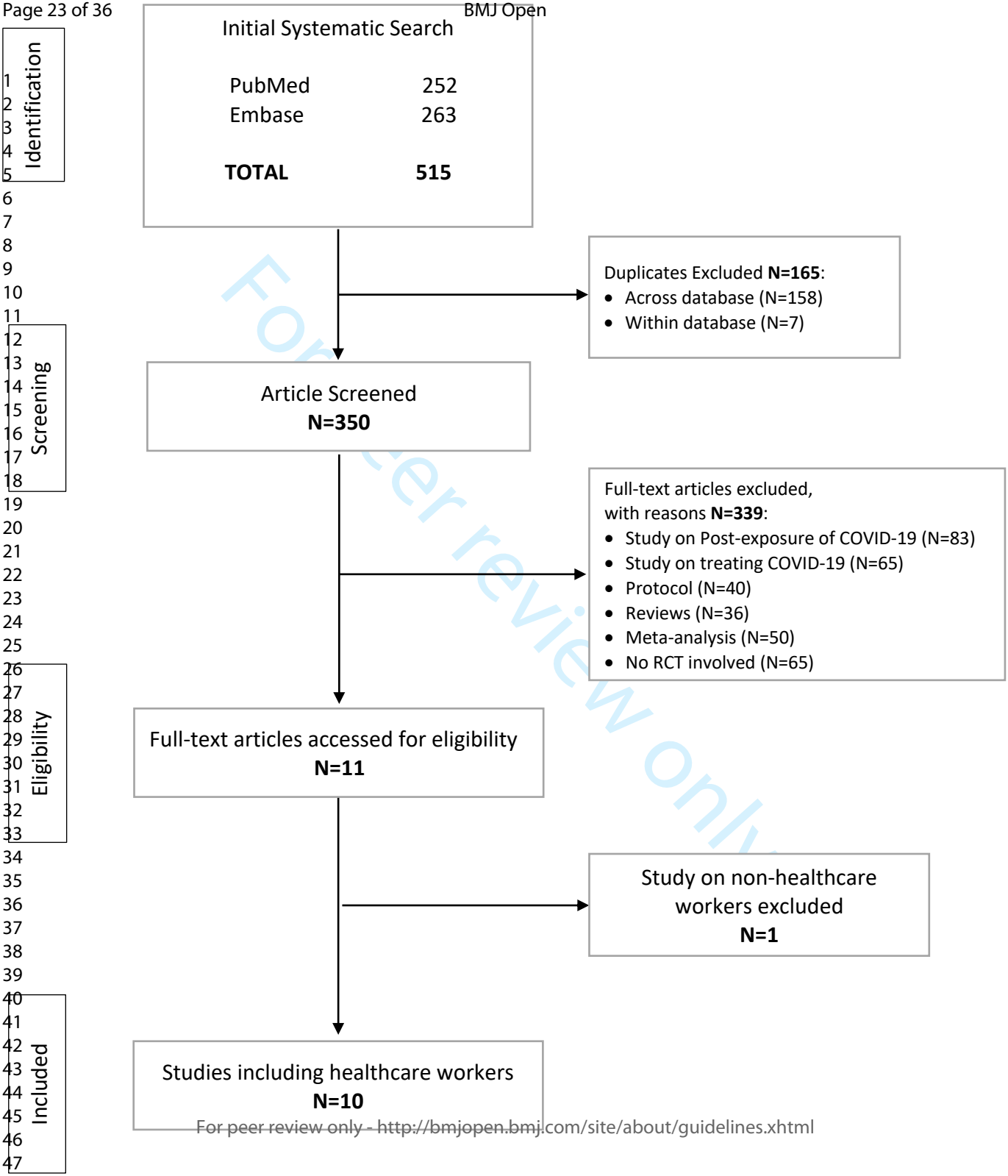
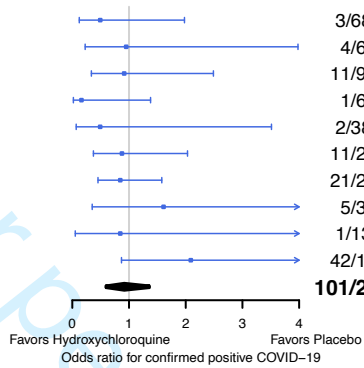
Figure Legends

Figure 1. Flowchart of literature review

Figure 2. Forest plots of the meta-analysis results showing the number of events (y), sample size (n), posterior median of odds ratios, and the associated 95% credible intervals comparing HCQ versus placebo for (a) lab-confirmed positive COVID-19, (b) suspected COVID-19, and (c) adverse events.



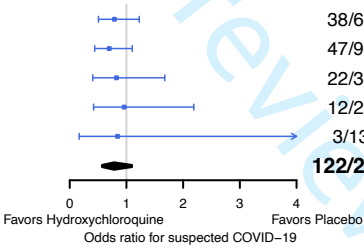
(a) Lab-confirmed positive COVID-19



Study	HCQ y/n	Placebo y/n	Odds Ratio [95%CI]
Naggie et al.	3/683	6/676	0.49 [0.12, 1.98]
Abella et al.	4/64	4/61	0.95 [0.23, 3.98]
Rajasingham et al.	11/989	6/494	0.91 [0.34, 2.49]
Rojas−Serrano et al.	1/62	6/65	0.16 [0.02, 1.38]
McKinnon et al.	2/387	2/191	0.49 [0.07, 3.51]
Vijayaraghavan et al.	11/211	12/203	0.88 [0.37, 2.03]
Polo et al.	21/224	23/211	0.85 [0.45, 1.58]
Llanos−Cuentas et al.	5/34	3/31	1.61 [0.35, 7.38]
Grau−Pujol et al.	1/137	1/116	0.85 [0.05, 13.67]
Syed et al.	42/154	7/46	2.09 [0.87, 5.03]
Meta-analysis	**101/2945**	**70/2094**	**0.92 [0.58, 1.37]**

I^2 = 0%

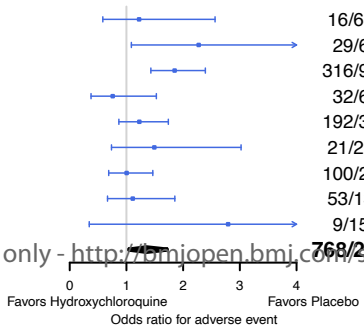
(b) Suspected COVID-19



Study	HCQ y/n	Placebo y/n	Odds Ratio [95% CI]
Naggie et al.	38/683	47/676	0.78 [0.51, 1.23]
Rajasingham et al.	47/989	33/494	0.70 [0.44, 1.10]
McKinnon et al.	22/387	13/191	0.83 [0.41, 1.68]
Vijayaraghavan et al.	12/211	12/203	0.96 [0.42, 2.19]
Grau−Pujol et al.	3/137	3/116	0.84 [0.17, 4.26]
Meta-analysis	**122/2407**	**108/1680**	**0.78 [0.57, 1.10]**

I^2 = 0%

(c) Adverse events



Study	HCQ y/n	Placebo y/n	Odds Ratio [95% CI]
Naggie et al.	16/683	13/676	1.22 [0.58, 2.56]
Abella et al.	29/65	17/65	2.27 [1.09, 4.76]
Rajasingham et al.	316/989	100/494	1.85 [1.43, 2.39]
Rojas−Serrano et al.	32/62	38/65	0.76 [0.38, 1.53]
McKinnon et al.	192/387	85/191	1.23 [0.87, 1.74]
Vijayaraghavan et al.	21/211	14/203	1.49 [0.74, 3.02]
Polo et al.	100/224	94/211	1.00 [0.69,1.47]
Grau−Pujol et al.	53/137	42/116	1.11 [0.67, 1.85]
Syed et al.	9/154	1/46	2.79 [0.34, 22.65]
Meta-analysis	**768/2912**	**404/2067**	**1.35 [1.03, 1.73]**

I^2 = 43%

Supplementary Materials

CONTENTS

eTable 1. Search code that was used to identify publications as of March 14, 2023

PubMed search

#1	covid[Title] OR coronavirus[Title] OR sars-cov-2[Title]
#2	hydroxychloroquine[Title]
#3	randomized[Title/Abstract] OR randomized[Title/Abstract]
#4	#1 AND #2 AND #3

Embase search

#1	covid:ti OR coronavirus:ti OR 'sars cov 2':ti
#2	hydroxychloroquine:ti
#3	randomized:ab,ti OR randomised:ab,ti
#4	#1 AND #2 AND #3

eTable 2. Risk of bias for trials included in the meta-analysis using the Cochrane risk assessment tool. Green circle is for low risk and yellow circle is for some concerns

	Selection bias (Randomization process)	Performance bias (Deviations from the intended interventions)	Attrition bias[1] (Missing outcome data)	Reporting bias (Measurement of the outcome)	Other sources of bias (Selection of the reported result)
Naggie et al. (HERO-HCQ)					
Abella et al. (PATCH)					
Rajasingham et al. (MN-COVID-PREP)					
Rojas-Serrano et al.					
McKinnon et al. (WHIP)					
Vijayaraghavan et al.					
Polo et al. (EPICOS)					
Llanos-Cuentas et al.					
Grau-Pujol et al.					
Syed et al.					

[1] The Rojas-Serrano et al. study reported minimal loss to follow-up (<10%). The Rojas-Serrano et al. study reported 18% (25/130) lost to follow-up and additional 12% (16/130) discontinued the intervention.

eTable 3. Characteristics of trials included in the meta-analysis

	Naggie et al. (HERO-HCQ)	Abella et al. (PATCH)	Rajasingham et al. (MN-COVID-PREP)	Rojas-Serrano et al.	McKinnon et al. (WHIP)
N (randomization)	1360	132	1496	130	624
Study start date[1]	4/22/2020	4/9/2020	4/6/2020	4/21/2020	4/10/2020
Study completion date[2]	1/9/2021	11/13/2020	7/13/2020	3/31/2021	12/14/2020
Occupation	HCWs at risk of COVID exposure through work in the ICU, emergency department, emergency services, respiratory services or COVID unit	HCWs (Physicians, nurses, certified nursing assistants, emergency technicians, respiratory therapists) eligible working >20 hrs/week	HCWs (physicians, nurses, emergency medical technicians) with direct contact with COVID patients including emergency department and ICU setting, first responders and performing aerosol generating procedures	HCWs (nurses, nursing aids, cleaning staff, orderlies, respiratory therapists and physicians) taking care of hospitalized patients with COVID	HCW, first responders and correlational/law officers, nursing home workers, medical students, public transit workers, household family members of HCW in Michigan and Ohio
Sites	34 sites across the US	2 tertiary urban hospitals	Multiple sites nationwide across US and Canada	Single site (National Institute of Respiratory Diseases of Mexico)	Multiple sites at Michigan in the US
Randomization	Yes (Phase III)	Yes (Phase II)	Yes (Phase III)	Yes (Phase III)	Yes (Phase III)
Trial type	Double-blinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	No weight requirement	<40kg excluded	<50kg excluded	N/A
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Excluded	Excluded	Excluded	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Included	Exclude
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Included	
Significant renal disease (stage IV or greater)	Excluded	Included	Excluded	Excluded	Exclude
Pregnant/breastfeeding	Included	Excluded	Included in US, Excluded in Canada	Excluded	Exclude
Medication					
Qtc prolonging medications	Excluded	Excluded	Excluded	Included	Exclude
Use of other medications with significant drug interactions	Included	Excluded	Excluded	Included	N/A
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine or azithromycin)	Any treatment for COVID-19 within 14 days excluded	Current use of HCQ or chloroquine excluded	HCQ or chloroquine within 30 days excluded	Chronic use of HCQ included
COVID-19 related criteria					
Active or prior COVID	Excluded	N/A	Excluded	Excluded	Excluded
Fevers, cough, SOB	Excluded	Excluded if symptoms within 2 weeks unless negative COVID test	Excluded	Excluded	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	N/A
Positive COVID serology	Included	Included	N/A	Included	N/A
Analysis	Modified intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat

	Vijayaraghavan et al.	Polo et al. (EPICOS)	Llanos-Cuentas et al.	Grau-Pujol et al.	Syed et al.
N (randomization)	416	454	68	269	200
Study start date[1]	6/29/2020	4/2020 Spain, 10/2020 Bolivia, 3/2021 Venezuela	June, 2020	4/4/2020	5/1/2020
Study completion date[2]	2/4/2021	5/30/2021	November, 2020	Study halted a 1 month analysis	Not reported
Occupation	HCWs in an environment with exposure to COVID-19 (physicians, nurses, allied health workers and ancillary health workers)	HCWs (physicians, nurses, medical students, other workers with and without direct patient contact)	HCWs (physicians, nursing staff, technical staff and nursing assistants involved in care of COVID-19 patients)	HCWs (physicians, nurses, nurse assistants and administrators working at least 3 days a week in the trial hospitals)	HCWs at risk of COVID-19 exposure including physicians, nurses, first responders, those performing aerosol generating procedures or working in the emergency department, ICU, and general medicine wards
Sites	9 hospitals across India	Multiple sites across Spain, Venezuela and Bolivia	4 public hospitals across the Lima metropolitan area	3 hospitals in Barcelona, Spain	Single hospital in Pakistan
Randomization	Yes	Yes	Yes (Phase III)	Yes	Yes (Phase II)
Trial type	Unblinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18-70	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	<40kg excluded	No weight requirement	No weight requirement	<40 kg
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Included	Excluded	Included	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Excluded	Excluded
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Excluded	Excluded
Significant renal disease (stage IV or greater)	Included	Excluded	Excluded	Excluded	Excluded
Pregnant/breastfeeding	Excluded	Excluded	Included	Excluded	Excluded
Medication					
Qtc prolonging medications	Excluded	Excluded	Included	Excluded	Excluded
Use of other medications with significant drug interactions	Excluded	Included	Included	Excluded	Excluded
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine azithromycin)	Any medication as prophylaxis against COVID-19 after 3/1/21	Use of hydroxychloroquine, chloroquine or azithromycin in the last 30 days excluded	Treatment with chloroquine or hydroxychloroquine within the last 1 month	Those already taking hydroxychloroquine were excluded
COVID-19 related criteria					
Active or prior COVID	Excluded	Excluded	Excluded	Excluded	Excluded
Fevers, cough, SOB	Not specified in exclusion criteria	Excluded	Not specified in exclusion criteria	Not specified in exclusion criteria	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	Excluded
Positive COVID serology	N/A	N/A	N/A	Excluded	Excluded
Analysis	Intention-to-treat	Not reported	Intention-to-treat	Intention-to-treat	Not reported

HCW=Healthcare workers; ICU=Intensive care unit; [1] Date when first participant was enrolled; [2] Date when final data were collected for the last participant

eTable 4. Definition of adverse events

Trial	AE definition
Naggie et al. (**HERO-HCQ**)	Adverse events include general disorders and administration site conditions, psychiatric disorders, skin and subcutaneous tissue disorders, cardiac disorders, infections and infestations, nervous system disorders, gastrointestinal disorders, investigations (electrocardiogram QT prolonged and heart rate increased), ear and labyrinth disorders, renal and urinary disorders, and respiratory, thoracic and mediastinal disorders.
Abella et al. (**PATCH**)	Adverse events include abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness.
Rajasingham et al. (**MN-COVID-PREP**)	Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and others.
Rojas-Serrano et al.	Examples of adverse events are as follows: abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness. Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and other.
McKinnon et al. (**WHIP**)	Covid-19 related symptoms, covid-19 clinical disease and medication adverse effects including gastrointestinal disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, cardiac disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, skin and subcutaneous tissue disorders, ear and labyrinth disorders, and eye disorders.
Vijayaraghavan et al.	Adverse events listed in each category at the participant level were categorized as cardiac, gastro-intestinal, headache, and Qtc prolongation.
Polo et al. (EPICOS)	Adverse events were classified by organ system and included: gastrointestinal disorders, blood and lymphatic system disorders, cardiac disorders, ear and labyrinth disorders, eye disorder, general disorders, immune system disorder, infections, injuries, investigations, metabolism and nutrition disorders, musculoskeletal/connective tissue disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system disorders, respiratory disorders, skin disorders and vascular disorders.
Llanos-Cuentas et al.	Adverse events from grade 1 to grade 3 and above. Note that the Llanos-Cuentas et al. study did report the number of adverse events (not participants) in the HCQ group only. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.
Grau-Pujol et al.	Adverse events included: general symptoms (fever, chills, sweating, malaise, myalgia, arthralgia), gastrointestinal symptoms (nausea, abdominal pain, diarrhea, dysgeusia), dermatological symptoms (itching, rash),respiratory symptoms (rhinorrhea, sore throat / odynophagia, cough, pleuritic pain, dyspnea), neurologic symptoms (headache, visual disturbances), and cardiovascular symptoms. Events were graded mild, moderate and severe.
Syed et al.	Syed et al. report the number of patients in each group who experienced adverse events, but did not report what the events were. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.

eTable 5. Baseline characteristics with additional variables and detailed information. Sample mean and standard deviation (in parenthesis) are reported for continuous variables, and the number of participants and proportion (in parenthesis) are reported for binary or categorical variables.

		Naggie et al. (HERO-HCQ)		Abella et al. (PATCH)		Rajasingham et al. (MN-COVID-PREP)		Rojas-Serrano et al.		McKinnon et al. (WHIP)	
		HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo	HCQ	Placebo	HCQ[1]	Placebo
	N (randomization)	683	676	66	66	989	494	62	65	387	191
	Age	44.2 (11.9)	43.1 (11.2)	31 (20-66)[3]	34 (23-62)[3]	41.5 (35, 49)[3]	40 (34, 48)[3]	31.0 (26.4-39)[4]	31.9 (27.2-43.7)[4]	45.7 (11.6); 44.9 (11.4)[2]	44.1 (12.7)
	Female	442 (64.7%)	446 (66.0%)	54 (82%)	37 (56%)	519 (52.5%)	241 (48.8%)	29 (42.6%)	42 (64.6%)	220 (57%)	114 (60%)
	BMI (kg/m^2)	28.3 (6.3)	28.6 (6.7)	26 (19-37)[5]	26 (20-50)[5]			26.7 (3.9)	27.2 (4.6)		
	Current smoker			0 (0%)	0 (0%)	38 (3.84%)	13 (2.6%)	20 (32.2%)[6]	23 (35.4%)[6]		
Race/ Ethnicity	White	624 (91.4%)	610 (90.2%)	55 (83%)	54 (82%)	852 (86.1%)	419 (84.8%)			334 (86%)	161 (84%)
	Asian			7 (11%)	7 (11%)	46 (4.7%)	29 (5.9%)			23 (6%)	15 (8%)
	African American	18 (2.6%)	23 (3.4%)	3 (4%)	1 (2%)	10 (1.0%)	10 (2.0%)			15 (4%)	9 (5%)
	Hispanic	39 (5.7%)	40 (5.9%)	0 (0%)	2 (3%)	40 (4.0%)	18 (3.6%)			11 (3%)	7 (4%)
Comorbidities	Asthma	58 (8.5%)	77 (11.4%)	9 (14%)	14 (21%)	91 (9.2%)	59 (11.9%)				
	Diabetes	20 (2.9%)	35 (5.2%)	1 (2%)	3 (5%)	36 (3.6%)	14 (2.8%)				
	Hypertension	99 (14.5%)	99 (14.6%)	3 (5%)	14 (21%)	145 (14.7%)	60 (12.1%)				
	None			54 (82%)	40 (61%)	646 (65.3%)	336 (68.0%)	53 (85.5%)	58 (89.2%)		
Practice Location	Emergency Department	96 (14.1%)	94 (13.9%)	38 (58%)	36 (55%)	417 (42.2%)	190 (38.5%)			48 (12%)	19 (10%)
	Internal Medicine ward			17 (26%)	18 (27%)	98 (9.9%)	56 (11.3%)			31 (8%)	20 (10%)
	ICU/anesthesia			6 (9%)	6 (9%)						
	Labor and delivery			5 (7%)	6 (9%)						
	Ambulance	66 (9.7%)	63 (9.3%)			73 (7.4%)	45 (9.1%)				
	Congregate care setting					46 (4.7%)	20 (4.0%)				
	ICU	48 (7.0%)	59 (8.7%)			184 (18.6%)	85 (17.2%)			37 (10%)	23 (12%)
	Operating room					103 (10.4%)	75 (15.2%)				
	EMS, Fire and Police First Responders									32 (8%)	16 (8%)
Occupation	Nurse	186/677 (27.5%)	167/668 (25.0%)	46 (70%)	42 (64%)						
	Physician	143/677 (21.1%)	144/668 (21.6%)	11 (17%)	16 (24%)						
	Certified Nurse Assistant			2 (3%)	2 (3%)						
	ED Technician			3 (4%)	1 (2%)						
	Respiratory therapist	15/677 (2.2%)	18/668 (2.7%)	3 (4%)	5 (7%)						
	Nurse or Physician							31 (50%)	33 (50.8%)		
	Emergency Medicine Provider					407 (41.1%)	190 (38.5%)				
	ICU provider					160 (16.2%)	83 (16.8%)				
	Anesthesia/ENT					178 (18.0%)	105 (21.3%)				
	HCW in COVID unit					76 (7.7%)	29 (5.9%)				
	Healthcare worker in congregate care setting					11 (1.1%)	4 (0.8%)				
	First responder					115 (11.6%)	65 (13.2%)				

		Vijayaraghavan et al.		Polo et al. (EPICOS)		Llanos-Cuentas et al.		Grau-Pujol et al.		Syed et al.	
		HCQ	Placebo	HCQ[2]	Placebo	HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo
	N (randomization)	213	203	231	223	36	32	142	127	154	46
	Age	32.3 (9.65)	31.8 (8.63)	38 (18-65)	38 (18,65)	39.14 (1.53)	39.28 (1.72)	39.6 (11.2)	40.3 (12.8)	30.25 (NA)	31.9 (9.13)
	Female	100 (46.9%)	97 (47.8%)	149 (64.5%)	143 (64.1%)	20 (55.6%)	20 (62.5%)	104 (73.2%)	93 (73.2%)	68 (44.1%)	23 (50%)
	BMI (kg/m^2)										
	Current smoker	8 (3.8%)	9 (4.4%)					21 (14.9%)	17 (13.8%)	19 (12.3%)	7 (15.2%)
Race/ Ethnicity	White										
	Asian										
	African American										
	Hispanic										
Comorbidities	Asthma	0 (0%)	0 (0%)	20 (8.7%)	9 (4.0%)	3 (8.3%)	4 (12.5%)	5 (3.5%)	2 (1.6%)		
	Diabetes	7 (3.3%)	3 (1.5%)	1 (0.4%)	3 (1.3%)	1 (2.8%)	0 (0%)	0 (0%)	1 (0.8%)	4 (2.6%)	3 (6.5%)
	Hypertension	2 (0.9%)	3 (1.5%)	4 (1.7%)	19 (8.5%)	3 (8.3%)	2 (6.3%)	2 (1.4%)	3 (2.4%)	7 (4.5%)	2 (4.3%)
	None										
Practice Location	Emergency Department	26 (12.2%)	18 (8.9%)	20 (8.7%)	21 (9.4%)						
	Internal Medicine ward	130 (64%)	130 (61%)								
	ICU/anesthesia										
	Labor and delivery										
	Ambulance			0 (0%)	0 (0%)						
	Congregate care setting										
	ICU	53 (24.9%)	53 (26.1%)	17 (7.4%)	13 (5.8%)						
	Operating room										
	EMS, Fire and Police First Responders										
Occupation	Nurse	67 (31.5%)	68 (33.5%)	67 (29.0%)	72 (32.3%)	6 (16.7%)	5 (15.6%)	35 (27.8%)	40 (28.2%)	20 (13.0%)	9 (19.6%)
	Physician	34 (16%)	31 (15.3%)	74 (32%)	66 (29.6%)	23 (63.9%)	16 (50%)	67 (47.2%)	53 (42.1%)	118 (76.6%)	25 (54.3%)
	Certified Nurse Assistant					1 (2.8%)	0 (0%)	12 (8.5%)	12 (9.5%)		
	ED Technician										
	Respiratory therapist										
	Nurse or Physician										
	Emergency Medicine Provider									2 (1.3%)	0 (0%)
	ICU provider										
	Anesthesia/ENT										
	HCW in COVID unit										
	Healthcare worker in congregate care setting										
	First responder									2 (1.3%)	0 (0%)

HCQ=Hydroxychloroquine ; ITT= Intention-to-treat ; BMI=Body mass index ; ICU=Intensive care unit; ED=Emergency department ; ENT=Ear, nose, throat ; HCW=Healthcare worker

[1] More than one HCQ groups with different doses are lumped.

[2] The Polo et al. study randomized participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.

[3] Median (range)

[4] Median (IQR)

[5] Mean (range)

[6] Current or previous smoker

eTable 6. Results of outcome measures in trials included in the meta-analysis. Sample size and the number of participants who had each outcome are reported with proportions (%) in parentheses.

	Treatment	N (ITT)	Confirmed COVID-19	Suspected with COVID compatible symptoms	Adverse event[2]
Naggie et al. (HERO-HCQ)	HCQ	683	3 (0.4)	38 (5.6)	16 (2.3)
	Placebo	676	6 (0.9)	47 (7.0)	13 (1.9)
Abella et al. (PATCH)	HCQ	64	4 (6.3)		29 (45.3)
	Placebo	61	4 (6.6)		17 (27.9)
Rajasingham et al. (MN-COVID-PREP)	HCQ[1]	989	11 (1.1)	47 (4.8)	316 (32.0)
	Placebo	494	6 (1.2)	33 (6.7)	100 (20.2)
Rojas-Serrano et al.	HCQ	62	1 (1.6)		32 (51.6)
	Placebo	65	6 (9.2)		38 (58.5)
McKinnon et al. (WHIP)	HCQ[1]	387	2 (0.5)	22 (5.7)	192 (49.6)
	Placebo	191	2 (1.0)	13 (6.8)	85 (44.5)
Vijayaraghavan et al.	HCQ	211	11 (5.2)	12 (5.7)	21 (10.0)
	Placebo	203	12 (5.9)	12 (5.9)	14 (6.9)
Polo et al. (EPICOS)	HCQ	224	21 (9.4)		100 (44.6)
	Placebo	211	23 (10.9)		94 (44.5)
Llanos-Cuentas et al.	HCQ	34	5 (14.7)		
	Placebo	31	3 (9.7)		
Grau-Pujol et al.	HCQ	137	1 (0.7)	3 (2.2)	53 (38.7)
	Placebo	116	1 (0.9)	3 (2.6)	42 (36.2)
Syed et al.	HCQ[1]	154	42 (27.3)		9 (5.8)
	Placebo	46	7 (15.2)		1 (2.2)

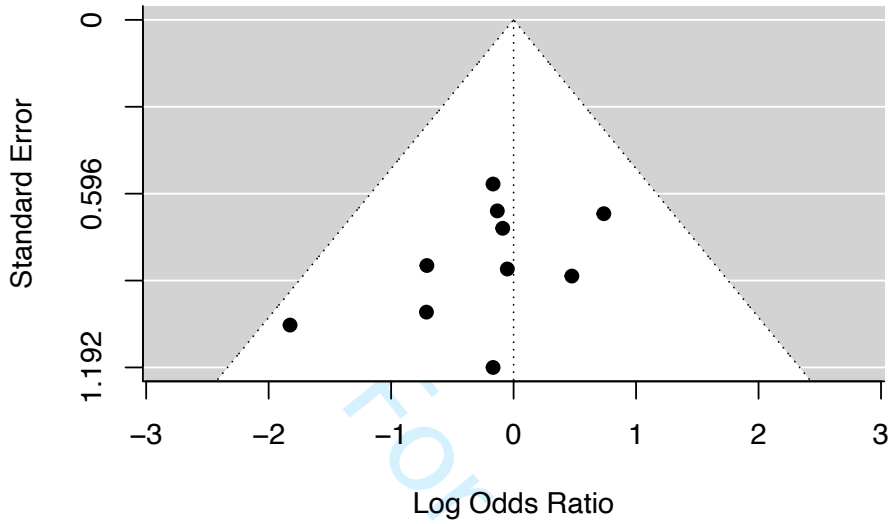
HCQ= Hydroxychloroquine; ITT= Intention-to-treat; AE=Adverse event ; COVID-RS=COVID-19 related symptoms ; Vit C= Vitamin C

[1] More than one HCQ groups with different doses are lumped.

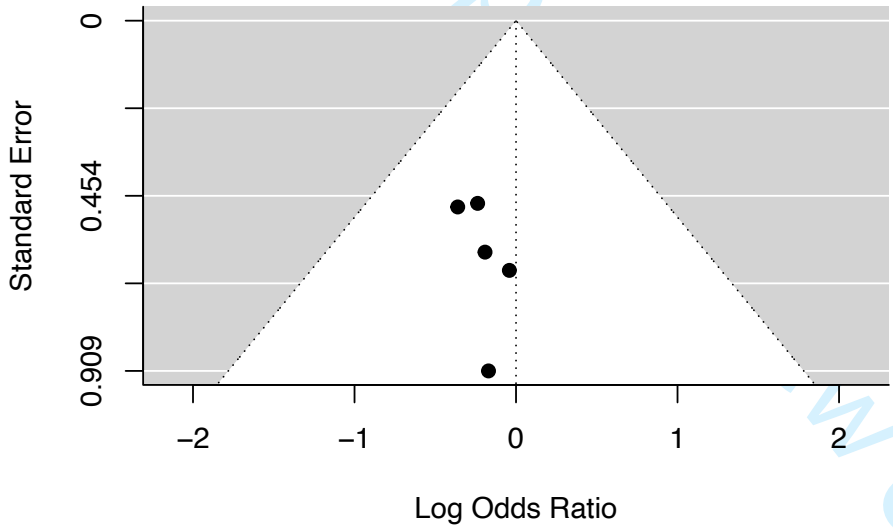
[2] Number of patients with any adverse events

eFigure. Funnel plots for the three outcomes

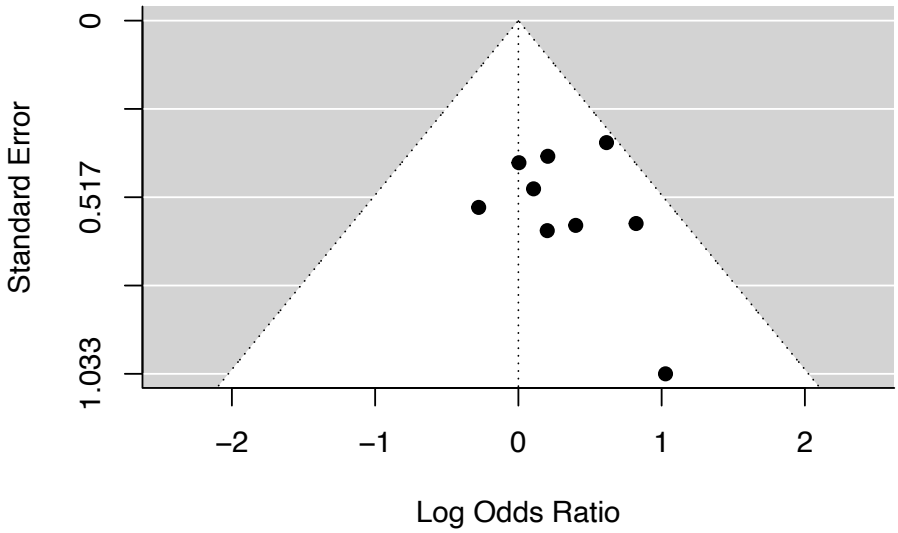
(a) Lab-confirmed positive COVID-19



(b) Suspected COVID-19



(c) Adverse events



eTable 7. Summary of GRADE score assessment

The summary table is applied to all three outcomes. The GRADE scores for the odds ratios with respect to all three outcomes were downgraded by 1 due to wide credible intervals of odds ratios, resulting in moderate certainty of evidence.

Item	Quality of evidence
Risk of bias	High
Inconsistency	High
Indirectness	High
Imprecision	Moderate
Publication bias	High

GRADE Working Group grades of evidence is available here: https://gdt.gradepro.org/app/handbook/handbook.html

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Supplement
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	11-12
Study characteristics	17	Cite each included study and present its characteristics.	8-9, Supplement
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplement
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplement
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11-13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplement
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplement
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14
	23b	Discuss any limitations of the evidence included in the review.	16
	23c	Discuss any limitations of the review processes used.	16
	23d	Discuss implications of the results for practice, policy, and future research.	16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Supplement
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplement

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomized clinical trials

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Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomized clinical trials

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Abstract

Objective: We studied the safety and efficacy of hydroxychloroquine (HCQ) as pre-exposure prophylaxis for COVID-19 in healthcare workers (HCWs), using a meta-analysis of randomized controlled trials.

Data Sources: PubMed, and EMBASE databases were searched to identify randomized trials studying HCQ.

Study Selection: Ten randomized controlled trials (RCTs) were identified (n=5,079 participants).

Data Extraction and Synthesis: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review and meta-analysis between HCQ and placebo using a Bayesian random-effects model. A *pre-hoc* statistical analysis plan was written, and the review protocol was registered at PROSPERO (CRD42021285093)

Main Outcomes: The primary efficacy outcome was polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection and the primary safety outcome was incidence of adverse events. The secondary outcome included clinically suspected SARS-CoV-2 infection.

Results: Compared with placebo, HCWs randomized to hydroxychloroquine (HCQ) had no significant difference in PCR-confirmed SARS-CoV-2 infection (odds ratio [OR] 0.92, 95% credible interval [CI]: 0.58, 1.37) or clinically suspected SARS-CoV-2 infection (OR 0.78, 95% CI: 0.57, 1.10), but significant difference in adverse events (OR 1.35, 95% CI: 1.03, 1.73).

Conclusions and Relevance: Our meta-analysis of ten RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs found that compared with placebo HCQ does not significantly reduce the risk of confirmed or clinically suspected SARS-CoV-2 infection, while HCQ significantly increases adverse events.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Bayesian meta-analysis models with random effects fitted the data.
- The ten trials included in the meta-analysis represent wide geographical locations including US, Canada, Mexico, India, Spain, Bolivia, Venezuela, Peru, and Pakistan.
- The findings can be applied to healthcare workers but should not be generalized to a broader population.

INTRODUCTION

Early during the SARS-CoV-2 pandemic, based on *in vitro* antiviral activity of both chloroquine and hydroxychloroquine against SARS-CoV-2 [1-3], clinicians considered use of hydroxychloroquine (HCQ) for treatment and prevention of SARS-CoV-2 infection and the associated disease, COVID-19. While there are now published randomized controlled trials of HCQ for the treatment of COVID-19 in the inpatient and outpatient setting [4, 5], there remains a lack of adequately powered randomized controlled trials of HCQ for the pre-exposure prophylaxis (PrEP) of SARS-CoV-2 infection. A number of COVID-19 clinical studies including PrEP studies were planned early in the pandemic; however, several never opened to enrollment and those that did open were closed early without reaching full accrual due to the rapidly changing landscape of preventative therapies, including vaccines, and a significant shift in public opinion of HCQ as a medical intervention for SARS-CoV-2 [6].

Vaccination access remains insufficient globally [7]. Specifically, in low-income countries only 33% of healthcare workers are fully vaccinated. While high-income countries have better coverage, overall 38% of countries did not achieve the milestone of 70% vaccination

coverage for healthcare workers by the end of 2021[8]. Thus, studying the pre-exposure prophylaxis potential for a drug with a known safety profile is crucial to protect people at high risk of exposures, such as healthcare workers (HCWs) [9, 10]. Two large randomized, placebo-controlled trials testing the safety and efficacy of HCQ as pre-exposure prophylaxis for COVID-19 in HCWs [11] [12], showed potential for a modest benefit of HCQ but were both underpowered, if a modest effect exists. More trials [13-15] studying HCQ as pre-exposure prophylaxis of COVID-19 in HCWs have been published with similar limitations.

To address the most common limitation, inadequate power to show a modest effect, we conducted a formal meta-analysis of pre-exposure prophylactic HCQ studies in HCWs. We conducted a systematic search for clinical trials of pre-exposure prophylactic use of HCQ against infection of SARS-CoV-2 in HCWs, thoroughly compared similarities and differences in characteristics of the identified studies and performed a Bayesian meta-analysis to combine results of the trials.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review and meta-analysis[16]. A statistical analysis plan was written in advance and the review protocol was registered at PROSPERO (CRD42021285093).

Search strategy and information sources

We searched PubMed/Medline and Ovid/Embase databases from database inception through the final search date March 14, 2023. We used keywords related to COVID-19, HCQ, and randomized controlled trials. The full search strategies are provided in eTable 1.

Eligibility criteria and study selection

The eligibility criteria included phase II or phase III randomized controlled trials (RCTs) of hydroxychloroquine for use as pre-exposure prophylaxis in HCWs with moderate to high risk of exposure. We excluded observational studies, crossover trials, studies where the method of allocation to treatment was not truly random, duplicate studies, and non-original data studies. No language, publication date, or publication status restrictions were applied. References of prior systematic reviews and meta-analyses were also screened for related studies. Study selection involved screening of titles and abstracts followed by full-text evaluation of possible eligible studies.

Data collection process

Each of the selected studies were independently reviewed by two reviewers (AF, MH, or HH). We extracted data on the study design, baseline characteristics, interventions, and outcomes. Any disagreements of collected information between reviews were reconciled through discussion by all three reviewers.

Outcome measures

The primary efficacy outcome for the meta-analysis was laboratory confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) test and the primary safety outcome was incidence of adverse events (Table 1). The secondary efficacy outcome was suspected or probable SARS-CoV-2 infection. Included studies had the following outcome definitions: (1) laboratory confirmed SARS-CoV-2 infection defined as COVID-19 like symptoms and positive SARS-

CoV-2 PCR and (2) suspected or probable SARS-CoV-2 infection defined as COVID-19 like symptoms but lack of confirmatory PCR testing.

Table 1. Treatment strategies, adherence, trial-defined primary outcome, and study duration for trials included in the meta-analysis

	Trial-defined primary outcome	Study duration	Treatment group	Randomized treatment assignment	Randomized sample size
Naggie et al.[13] (HERO-HCQ)	Confirmed (by NP swab PCR) or suspected COVID-19 infection through 30 days	60 days	HCQ Control	HCQ 600 mg BID loading dose for Day 1, followed by 400 mg QD for 29 days Placebo	683 676
Abella et al.[11] (PATCH)	COVID-19 infection as determined by positive NP swab over 8 weeks	56 days (8 weeks)	HCQ Control	HCQ 600mg daily for 60 days Placebo	64 61
Rajasingham et al.[12] (MN-COVID-PREP)	COVID-19 free survival time by lab confirmed or probable illness	84 days (12 weeks)	HCQ[a] Control	HCQ loading doses (400 mg twice 6-8hrs apart), followed by 400 mg once weekly or 400 mg twice weekly for 84 days Placebo	989 494
Rojas-Serrano et al.[14]	Time to symptomatic respiratory infection with a positive COVID RT PCR over 60 days	60 days	HCQ Control	HCQ 200 mg daily for 60 days Placebo	62 65
McKinnon et al.[15] (WHIP)	Lab confirmed cases of COVID-19 determined by either IgM and IgG serology in blood sample or RT-PCR test results Confirmed new cases of COVID-19	56 days (8 weeks)	HCQ[a] Control	HCQ 400 mg loading dose for Day 1, followed by 200 mg daily or 400 mg weekly on the same day of each week for 56 days Placebo	387 191
Vijayaraghavan et al.[17]	Lab confirmed SARS-CoV-2 infection by PCR or presence of antibodies	180 days (6 months)	HCQ Control	HCQ 400 mg twice on the day of enrollment, followed by 400 mg once a week for a total of 12 weeks plus personal protective equipment (PPE) PPE	213 203
Polo et al.[18] (EPICOS)	Lab confirmed symptomatic COVID-19 by PCR	84 days (12 weeks)	HCQ[b] Control	HCQ 200 mg once daily Placebo	231 223
Llanos-Cuentas et al.[19]	COVID-19 cases confirmed by PCR or serological test	28 days (4 weeks)	HCQ Control	HCQ loading dose of 600 mg on the first day, followed by 400 mg every other day plus PPE PPE	36 32
Grau-Pujol et al.[20]	COVID-19 confirmed cases with	180 days (6 months)	HCQ	HCQ 400 mg daily for the four consecutive	142

	PCR test			days, followed by 400 mg weekly	
			Control	Placebo	127
Syed et al.[17]	COVID-19-free survival (COVID-19 confirmed by PCR)	84 days (12 weeks)	HCQ[a]	HCQ 400 mg twice for Day 1, followed by 400 weekly or HCQ 400 mg once every 3 weeks or HCQ 200 mg once every 3 weeks	154
			Control	Placebo	46

HCQ=Hydroxychloroquine

[a] More than one HCQ groups with different doses are lumped.

[b] The Polo et al. study randomized participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.

Treatment assignment

Our meta-analysis did not study HCQ dosing specific effects. For studies randomizing participants to more than one HCQ arm with different doses, all HCQ arms were merged and considered as a single HCQ arm. Such studies include the Rajasingham et al., McKinnon et al. and Syed et al. studies.

Risk of bias and certainty of evidence assessment

Two independent reviewers (AF, HH) assessed the risk of bias (low, intermediate, high) of the included studies using the Cochrane's Collaboration tool [21] (eTable 2). We assessed the certainty of evidence using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach [22].

Statistical analysis

Bayesian logistic regression meta-analysis models under two assumptions (fixed effect and random effects) were fitted to estimate the odds ratio of having an outcome between hydroxychloroquine and placebo [23]. The fixed effect model assumes that the odds ratio is constant across studies, while the random effects model accounts for heterogeneity in the odds

ratios across studies. To assess and compare the goodness-of-fit of the fitted fixed and random effects models, we calculated the Watanabe-Akaike information criterion [24]. In the Bayesian models, we assigned non-informative prior distributions as no prior information was available. The odds ratios and the associated 95% credible intervals were estimated using Markov chain Monte Carlo (MCMC) algorithms. In addition, we calculated Bayesian posterior probabilities of the odds ratio smaller than 1 or 0.5 for the primary efficacy outcome, and greater than 2 for the safety outcome [25]. The standard deviation of the random effects and I^2 [26] were estimated to quantify the between-study heterogeneity, where small values of both metrics indicate slight heterogeneity. To identify publication bias, we plotted and assessed funnel plots for their symmetry, and conducted the Egger's test[27]. All Bayesian meta-analyses were conducted using the `rstan` package (version 2.21.2)[28] in R 4.0.2 [29]. We used two parallel chains, where each chain consists of 50,000 samples after a 25,000-sample burn-in. We checked convergence of the MCMC chains for all model parameters using trace plots and Gelman-Rubin diagnostic statistics [30].

Patient and public involvement

No patient involved.

RESULTS

Search results

Our database search resulted in 350 unique studies after excluding duplicates. Of those, 339 studies were screened out due to irrelevance based on title and abstract screening. Eleven studies were assessed in full-text for eligibility (Figure 1). Of those, one trial was excluded from the

meta-analysis because it studied with non-healthcare worker populations. As a result, a total of ten studies in a population consisting of HCWs were identified (Table 1).

Study and patient characteristics

Study design, population, treatment strategies, and key characteristics are presented in Table 1 and eTable 3. A total of 5,079 randomized participants (2,961 randomized to HCQ) from the 10 studies were included in the meta-analysis. The ten studies defined HCWs broadly and included first responders (emergency medical services, fire, and police). The follow-up duration of the 10 studies ranged from 28 days to 180 days. The HCQ dosing scheme varied across studies, including daily dosing ranging from 200 to 600mg daily with or without a loading dose and once or twice weekly or once every three weeks dosing. The duration of therapy also varied across studies (Table 1). The trial-specific definitions of primary outcome and adverse events are comparable across trials (Table 1, eTable 4).

Baseline characteristics by randomized treatment assignment are reported (eTable 5). The average age ranged between 31 and 45. The aggregate proportion of women within each study varied across the 10 trials, with a range from 44% to 69%. In addition, the Abella et al. and Rojas-Serrano et al. studies had smaller sample size compared with the other three studies and showed a difference in female ratio between placebo and HCQ groups. In the Naggie et al., Abella et al., Rajasingham et al., and McKinnon et al., studies, over 80% of study participants were white. The Abella et al. and Rajasingham et al. studies had high proportions of HCWs working in an emergency department (56% and 41%, respectively) and the Abella et al. study had a high proportion of nurses (67%).

Several studies reported treatment adherence assessed by two methods: self-reported adherence and/or pill count at the end of the study. The Rajasingham et al. study additionally conducted remote blood sampling to verify HCQ concentrations in a subset. Adherence varied significantly across the studies, with a low proportion of approximately 52% in the Rojas-Serrano et al. study and 97-98% in the Abella et al. study.

Results of meta-analysis

Overall, 3.4% (171/5039) developed PCR-confirmed SARS-CoV-2 infection and 5.6% (230/4087) developed suspected COVID-19 that was not laboratory confirmed. Since the goodness-of-fit assessment using Watanabe-Akaike information criterion concluded that the random effects meta-analysis model was as good as or better than the fixed effect meta-analysis model for all outcomes, we reported the results under the random effects model. Compared with placebo, HCWs randomized to HCQ had numerically lower rate of PCR-confirmed SARS-CoV-2 infection cases (odds ratio [OR] 0.92, 95% credible interval [CI]: 0.58, 1.37; GRADE score: moderate certainty), and suspected or probable SARS-CoV-2 infection cases (OR 0.78, 95% CI: 0.57, 1.10; GRADE score: moderate certainty). None of these odds ratios were statistically significant. Participants treated with HCQ had a numerically higher rate of adverse events (OR 1.35, 95% CI: 1.03, 1.73; GRADE score: moderate certainty) with statistical significance (Figure 2). The outcome data used in our analyses are presented in eTable 6. The summary of GRADE score assessment is provided in eTable 7.

The Bayesian posterior probabilities of the odds ratio less than 1 for the confirmed SARS-CoV-2 infection outcome (i.e., the probability of HCQ favoring over placebo) was 0.67, while the posterior probability of odds ratio less than 0.5 (i.e., the probability that the odds of having a confirmed SARS-CoV-2 infection outcome in HCQ is less than a half of the odds in placebo) was 0.009. The posterior probability of the odds ratio greater than 2 for the adverse event outcome (i.e., the probability that the odds of having an adverse event in HCQ is greater than twice of the odds in placebo) was 0.004.

Our meta-analysis showed little or moderate variability of effect estimates across studies with I^2 value of 0%, 0%, and 43%, and the estimated standard deviation of the random effects of 0.39, 0.26, and 0.45 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection, and adverse event outcomes, respectively. Funnel plots (eFigure) showed no indication of publication bias and the associated Egger's test results supported that the funnel plots were not asymmetry with p-values of 0.308, 0.305, and 0.794 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection, and adverse event outcomes, respectively.

DISCUSSION

Understanding the pre-exposure prophylactic effect of HCQ against COVID-19 remains relevant, as its use continues, particularly in the international setting [31, 32]. Our meta-analysis of the ten RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in 5,079 HCWs found that HCQ did not have a statistical association with fewer confirmed or suspected/probable SARS-CoV-2 infection cases compared with placebo. The geographical locations of the 10 trials included in the meta-analysis are US, Canada, Mexico, India, Spain,

Bolivia, Venezuela, Peru, and Pakistan (eTable 3). While the odds ratios of most studies favor HCQ, the credible intervals remain wide suggesting low certainty in the true point estimate. Two studies including the Llanos-Cuentas et al. study conducted in Peru and the Syed et al. study conducted in Pakistan showed odds ratios favoring placebo, though the credible intervals remain wide. Furthermore, in this population, COVID-19 events rates were low, particularly for the most relevant PCR-confirmed infection outcome. The low event rate raises further concern for the uncertainty of these outcomes. Thus, if there is a minimal effect, the absolute benefit would be low. To gain more certainty, a very large study would need to be done and this is difficult to support now due to availability of highly effective vaccines. The safety profile of HCQ in the outpatient setting is well understood [33]. In these outpatient studies there was statistically significant difference in adverse events in the HCQ versus the placebo arm, indicating that HCQ is less safe than placebo.

Our findings can be applied to HCWs but should not be generalized to a broader population. Our systematic search found only one published RCT of pre-exposure prophylaxis for non-healthcare worker populations and the study were excluded from our meta-analysis. This study was conducted in Singapore [34] and showed a significant reduction in the risk of COVID-19 infection in the HCQ arm when compared with the comparator arm, vitamin C. However, this study showed moderate risk of bias as it used an open-label cluster-randomization design, the Institutional Review Board excluded higher risk persons from the hydroxychloroquine arm only, and the participants may not be representative of a general population due to the communal living environment.

A Bayesian meta-analysis approach was used to fit the data. The Bayesian meta-analysis approach has several advantages. First, its flexibility and the MCMC sampling methods to estimate posterior distributions provide probability-based quantities (e.g., posterior probability of an odds ratio smaller than 0.5) that complement typical meta-analysis results (e.g., odds ratios and the associated credible intervals) and help decision making [35]. Second, the Bayesian meta-analysis model with random effects estimates the between-study variability better than the frequentist counterparts [36]. Third, when it comes to with binary outcomes, the Bayesian approach handles rare events better than the frequentist counterparts [23].

A recently published meta-analysis by García-Albéniz et al. [37] investigated pre-exposure (seven RCTs included) and post-exposure (four RCTs included) prophylactic effects of HCQ, but not limited to the HCW population. They found significant pre-exposure prophylactic effects of HCQ on SARS-CoV-2 infection, different from ours. The seven pre-exposure prophylaxis RCTs included in the García-Albéniz et al. meta-analysis consisted of six RCTs that were in our meta-analysis and the aforementioned Singapore study that was excluded from our meta-analysis. Our meta-analysis provides the most up-to-date, systematic, and comprehensive evidence about prophylactic effects of HCQ focusing on the HCW population.

Although a meta-analysis allows for combining evidence from multiple studies in a principled way, our meta-analysis has limitations. First, our analysis did not evaluate effects of different HCQ doses and combined multiple HCQ arms using different doses in three studies. The RCTs included in our meta-analysis studied varying dosing schemes and a meta-analysis using aggregate-level data is not a sufficient source to study dosing effects. Second, detailed subgroup

analyses were not conducted due to limited information. Individual-level data are required to study both dosing and subgroup effects.

Our meta-analysis of ten RCTs investigating safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs provides the most up-to-date evidence on HCQ. Although most individual trials were underpowered and showed null data, integrating the results systematically via meta-analysis contributes to the scientific literature and provides certain answers to the question. We found that HCQ does not reduce the risk of confirmed or probable SARS-CoV-2 infection, but increase risk of adverse events compared with placebo. Hydroxychloroquine should not be used for pre-exposure prophylaxis in the HCW population.

Contributors

All authors fulfill the ICMJE criteria for authorship. HH, SN, RR, and KJA designed the study. HH, AF, and MH collected and analyzed the data. HH, SN, and RR wrote the manuscript. SH and KJA provided statistical review and AF, JEM, RA, JRS, BSA, AMPV, CWW, AH and DRB provided clinical review. All authors approved and decided to submit the paper for publication.

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Competing interests

All authors except Dr. Abella reported no financial relationship with commercial interest. Dr. Abella have received NIH funds for COVID-19 related research, and holds equity in VOC Health, a start-up company that is developing novel covid testing.

Ethics Approval

Ethics approval was not required because this study used publicly available aggregate data that were not involved with patients' information or prospective data collection.

Data sharing statement

The data are presented in eTable 6.

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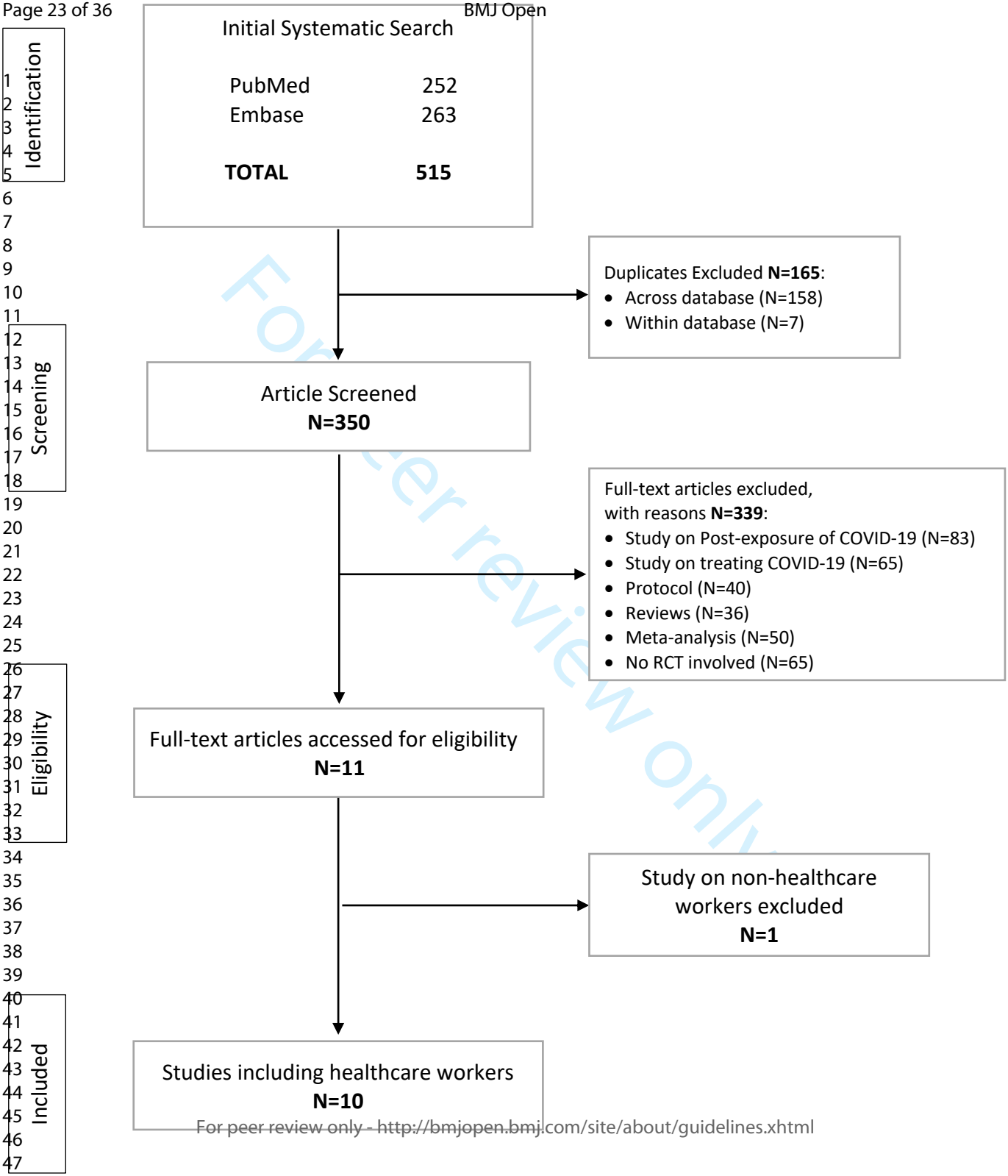
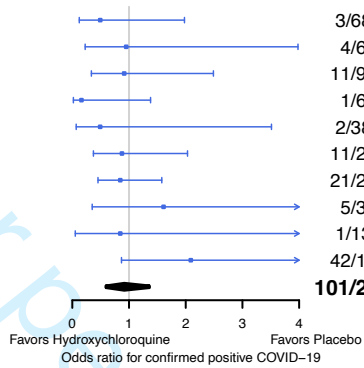
Figure Legends

Figure 1. Flowchart of literature review

Figure 2. Forest plots of the meta-analysis results showing the number of events (y), sample size (n), posterior median of odds ratios, and the associated 95% credible intervals comparing HCQ versus placebo for (a) lab-confirmed positive COVID-19, (b) suspected COVID-19, and (c) adverse events.



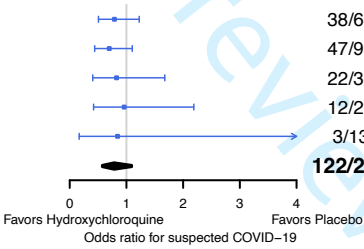
(a) Lab-confirmed positive COVID-19



Study	HCQ y/n	Placebo y/n	Odds Ratio [95%CI]
Naggie et al.	3/683	6/676	0.49 [0.12, 1.98]
Abella et al.	4/64	4/61	0.95 [0.23, 3.98]
Rajasingham et al.	11/989	6/494	0.91 [0.34, 2.49]
Rojas−Serrano et al.	1/62	6/65	0.16 [0.02, 1.38]
McKinnon et al.	2/387	2/191	0.49 [0.07, 3.51]
Vijayaraghavan et al.	11/211	12/203	0.88 [0.37, 2.03]
Polo et al.	21/224	23/211	0.85 [0.45, 1.58]
Llanos−Cuentas et al.	5/34	3/31	1.61 [0.35, 7.38]
Grau−Pujol et al.	1/137	1/116	0.85 [0.05, 13.67]
Syed et al.	42/154	7/46	2.09 [0.87, 5.03]
Meta-analysis	**101/2945**	**70/2094**	**0.92 [0.58, 1.37]**

I^2 = 0%

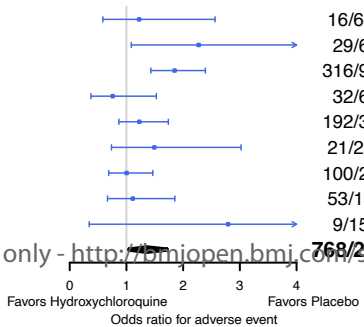
(b) Suspected COVID-19



Study	HCQ y/n	Placebo y/n	Odds Ratio [95% CI]
Naggie et al.	38/683	47/676	0.78 [0.51, 1.23]
Rajasingham et al.	47/989	33/494	0.70 [0.44, 1.10]
McKinnon et al.	22/387	13/191	0.83 [0.41, 1.68]
Vijayaraghavan et al.	12/211	12/203	0.96 [0.42, 2.19]
Grau−Pujol et al.	3/137	3/116	0.84 [0.17, 4.26]
Meta-analysis	**122/2407**	**108/1680**	**0.78 [0.57, 1.10]**

I^2 = 0%

(c) Adverse events



Study	HCQ y/n	Placebo y/n	Odds Ratio [95% CI]
Naggie et al.	16/683	13/676	1.22 [0.58, 2.56]
Abella et al.	29/65	17/65	2.27 [1.09, 4.76]
Rajasingham et al.	316/989	100/494	1.85 [1.43, 2.39]
Rojas−Serrano et al.	32/62	38/65	0.76 [0.38, 1.53]
McKinnon et al.	192/387	85/191	1.23 [0.87, 1.74]
Vijayaraghavan et al.	21/211	14/203	1.49 [0.74, 3.02]
Polo et al.	100/224	94/211	1.00 [0.69,1.47]
Grau−Pujol et al.	53/137	42/116	1.11 [0.67, 1.85]
Syed et al.	9/154	1/46	2.79 [0.34, 22.65]
Meta-analysis	**768/2912**	**404/2067**	**1.35 [1.03, 1.73]**

I^2 = 43%

Supplementary Materials

CONTENTS

eTable 1. Search code that was used to identify publications as of March 14, 2023

PubMed search

#1	covid[Title] OR coronavirus[Title] OR sars-cov-2[Title]
#2	hydroxychloroquine[Title]
#3	randomized[Title/Abstract] OR randomized[Title/Abstract]
#4	#1 AND #2 AND #3

Embase search

#1	covid:ti OR coronavirus:ti OR 'sars cov 2':ti
#2	hydroxychloroquine:ti
#3	randomized:ab,ti OR randomised:ab,ti
#4	#1 AND #2 AND #3

eTable 2. Risk of bias for trials included in the meta-analysis using the Cochrane risk assessment tool. Green circle is for low risk and yellow circle is for some concerns

	Selection bias (Randomization process)	Performance bias (Deviations from the intended interventions)	Attrition bias[1] (Missing outcome data)	Reporting bias (Measurement of the outcome)	Other sources of bias (Selection of the reported result)
Naggie et al. (HERO-HCQ)					
Abella et al. (PATCH)					
Rajasingham et al. (MN-COVID-PREP)					
Rojas-Serrano et al.					
McKinnon et al. (WHIP)					
Vijayaraghavan et al.					
Polo et al. (EPICOS)					
Llanos-Cuentas et al.					
Grau-Pujol et al.					
Syed et al.					

[1] The Rojas-Serrano et al. study reported minimal loss to follow-up (<10%). The Rojas-Serrano et al. study reported 18% (25/130) lost to follow-up and additional 12% (16/130) discontinued the intervention.

eTable 3. Characteristics of trials included in the meta-analysis

	Naggie et al. (HERO-HCQ)	Abella et al. (PATCH)	Rajasingham et al. (MN-COVID-PREP)	Rojas-Serrano et al.	McKinnon et al. (WHIP)
N (randomization)	1360	132	1496	130	624
Study start date[1]	4/22/2020	4/9/2020	4/6/2020	4/21/2020	4/10/2020
Study completion date[2]	1/9/2021	11/13/2020	7/13/2020	3/31/2021	12/14/2020
Occupation	HCWs at risk of COVID exposure through work in the ICU, emergency department, emergency services, respiratory services or COVID unit	HCWs (Physicians, nurses, certified nursing assistants, emergency technicians, respiratory therapists) eligible working >20 hrs/week	HCWs (physicians, nurses, emergency medical technicians) with direct contact with COVID patients including emergency department and ICU setting, first responders and performing aerosol generating procedures	HCWs (nurses, nursing aids, cleaning staff, orderlies, respiratory therapists and physicians) taking care of hospitalized patients with COVID	HCW, first responders and correlational/law officers, nursing home workers, medical students, public transit workers, household family members of HCW in Michigan and Ohio
Sites	34 sites across the US	2 tertiary urban hospitals	Multiple sites nationwide across US and Canada	Single site (National Institute of Respiratory Diseases of Mexico)	Multiple sites at Michigan in the US
Randomization	Yes (Phase III)	Yes (Phase II)	Yes (Phase III)	Yes (Phase III)	Yes (Phase III)
Trial type	Double-blinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	No weight requirement	<40kg excluded	<50kg excluded	N/A
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Excluded	Excluded	Excluded	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Included	Exclude
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Included	
Significant renal disease (stage IV or greater)	Excluded	Included	Excluded	Excluded	Exclude
Pregnant/breastfeeding	Included	Excluded	Included in US, Excluded in Canada	Excluded	Exclude
Medication					
Qtc prolonging medications	Excluded	Excluded	Excluded	Included	Exclude
Use of other medications with significant drug interactions	Included	Excluded	Excluded	Included	N/A
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine or azithromycin)	Any treatment for COVID-19 within 14 days excluded	Current use of HCQ or chloroquine excluded	HCQ or chloroquine within 30 days excluded	Chronic use of HCQ included
COVID-19 related criteria					
Active or prior COVID	Excluded	N/A	Excluded	Excluded	Excluded
Fevers, cough, SOB	Excluded	Excluded if symptoms within 2 weeks unless negative COVID test	Excluded	Excluded	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	N/A
Positive COVID serology	Included	Included	N/A	Included	N/A
Analysis	Modified intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat

	Vijayaraghavan et al.	Polo et al. (EPICOS)	Llanos-Cuentas et al.	Grau-Pujol et al.	Syed et al.
N (randomization)	416	454	68	269	200
Study start date[1]	6/29/2020	4/2020 Spain, 10/2020 Bolivia, 3/2021 Venezuela	June, 2020	4/4/2020	5/1/2020
Study completion date[2]	2/4/2021	5/30/2021	November, 2020	Study halted a 1 month analysis	Not reported
Occupation	HCWs in an environment with exposure to COVID-19 (physicians, nurses, allied health workers and ancillary health workers)	HCWs (physicians, nurses, medical students, other workers with and without direct patient contact)	HCWs (physicians, nursing staff, technical staff and nursing assistants involved in care of COVID-19 patients)	HCWs (physicians, nurses, nurse assistants and administrators working at least 3 days a week in the trial hospitals)	HCWs at risk of COVID-19 exposure including physicians, nurses, first responders, those performing aerosol generating procedures or working in the emergency department, ICU, and general medicine wards
Sites	9 hospitals across India	Multiple sites across Spain, Venezuela and Bolivia	4 public hospitals across the Lima metropolitan area	3 hospitals in Barcelona, Spain	Single hospital in Pakistan
Randomization	Yes	Yes	Yes (Phase III)	Yes	Yes (Phase II)
Trial type	Unblinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18-70	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	<40kg excluded	No weight requirement	No weight requirement	<40 kg
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Included	Excluded	Included	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Excluded	Excluded
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Excluded	Excluded
Significant renal disease (stage IV or greater)	Included	Excluded	Excluded	Excluded	Excluded
Pregnant/breastfeeding	Excluded	Excluded	Included	Excluded	Excluded
Medication					
Qtc prolonging medications	Excluded	Excluded	Included	Excluded	Excluded
Use of other medications with significant drug interactions	Excluded	Included	Included	Excluded	Excluded
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine azithromycin)	Any medication as prophylaxis against COVID-19 after 3/1/21	Use of hydroxychloroquine, chloroquine or azithromycin in the last 30 days excluded	Treatment with chloroquine or hydroxychloroquine within the last 1 month	Those already taking hydroxychloroquine were excluded
COVID-19 related criteria					
Active or prior COVID	Excluded	Excluded	Excluded	Excluded	Excluded
Fevers, cough, SOB	Not specified in exclusion criteria	Excluded	Not specified in exclusion criteria	Not specified in exclusion criteria	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	Excluded
Positive COVID serology	N/A	N/A	N/A	Excluded	Excluded
Analysis	Intention-to-treat	Not reported	Intention-to-treat	Intention-to-treat	Not reported

HCW=Healthcare workers; ICU=Intensive care unit; [1] Date when first participant was enrolled; [2] Date when final data were collected for the last participant

eTable 4. Definition of adverse events

Trial	AE definition
Naggie et al. (**HERO-HCQ**)	Adverse events include general disorders and administration site conditions, psychiatric disorders, skin and subcutaneous tissue disorders, cardiac disorders, infections and infestations, nervous system disorders, gastrointestinal disorders, investigations (electrocardiogram QT prolonged and heart rate increased), ear and labyrinth disorders, renal and urinary disorders, and respiratory, thoracic and mediastinal disorders.
Abella et al. (**PATCH**)	Adverse events include abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness.
Rajasingham et al. (**MN-COVID-PREP**)	Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and others.
Rojas-Serrano et al.	Examples of adverse events are as follows: abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness. Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and other.
McKinnon et al. (**WHIP**)	Covid-19 related symptoms, covid-19 clinical disease and medication adverse effects including gastrointestinal disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, cardiac disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, skin and subcutaneous tissue disorders, ear and labyrinth disorders, and eye disorders.
Vijayaraghavan et al.	Adverse events listed in each category at the participant level were categorized as cardiac, gastro-intestinal, headache, and Qtc prolongation.
Polo et al. (EPICOS)	Adverse events were classified by organ system and included: gastrointestinal disorders, blood and lymphatic system disorders, cardiac disorders, ear and labyrinth disorders, eye disorder, general disorders, immune system disorder, infections, injuries, investigations, metabolism and nutrition disorders, musculoskeletal/connective tissue disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system disorders, respiratory disorders, skin disorders and vascular disorders.
Llanos-Cuentas et al.	Adverse events from grade 1 to grade 3 and above. Note that the Llanos-Cuentas et al. study did report the number of adverse events (not participants) in the HCQ group only. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.
Grau-Pujol et al.	Adverse events included: general symptoms (fever, chills, sweating, malaise, myalgia, arthralgia), gastrointestinal symptoms (nausea, abdominal pain, diarrhea, dysgeusia), dermatological symptoms (itching, rash),respiratory symptoms (rhinorrhea, sore throat / odynophagia, cough, pleuritic pain, dyspnea), neurologic symptoms (headache, visual disturbances), and cardiovascular symptoms. Events were graded mild, moderate and severe.
Syed et al.	Syed et al. report the number of patients in each group who experienced adverse events, but did not report what the events were. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.

eTable 5. Baseline characteristics with additional variables and detailed information. Sample mean and standard deviation (in parenthesis) are reported for continuous variables, and the number of participants and proportion (in parenthesis) are reported for binary or categorical variables.

		Naggie et al. (HERO-HCQ)		Abella et al. (PATCH)		Rajasingham et al. (MN-COVID-PREP)		Rojas-Serrano et al.		McKinnon et al. (WHIP)	
		HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo	HCQ	Placebo	HCQ[1]	Placebo
	N (randomization)	683	676	66	66	989	494	62	65	387	191
	Age	44.2 (11.9)	43.1 (11.2)	31 (20-66)[3]	34 (23-62)[3]	41.5 (35, 49)[3]	40 (34, 48)[3]	31.0 (26.4-39)[4]	31.9 (27.2-43.7)[4]	45.7 (11.6); 44.9 (11.4)[2]	44.1 (12.7)
	Female	442 (64.7%)	446 (66.0%)	54 (82%)	37 (56%)	519 (52.5%)	241 (48.8%)	29 (42.6%)	42 (64.6%)	220 (57%)	114 (60%)
	BMI (kg/m^2)	28.3 (6.3)	28.6 (6.7)	26 (19-37)[5]	26 (20-50)[5]			26.7 (3.9)	27.2 (4.6)		
	Current smoker			0 (0%)	0 (0%)	38 (3.84%)	13 (2.6%)	20 (32.2%)[6]	23 (35.4%)[6]		
Race/ Ethnicity	White	624 (91.4%)	610 (90.2%)	55 (83%)	54 (82%)	852 (86.1%)	419 (84.8%)			334 (86%)	161 (84%)
	Asian			7 (11%)	7 (11%)	46 (4.7%)	29 (5.9%)			23 (6%)	15 (8%)
	African American	18 (2.6%)	23 (3.4%)	3 (4%)	1 (2%)	10 (1.0%)	10 (2.0%)			15 (4%)	9 (5%)
	Hispanic	39 (5.7%)	40 (5.9%)	0 (0%)	2 (3%)	40 (4.0%)	18 (3.6%)			11 (3%)	7 (4%)
Comorbidities	Asthma	58 (8.5%)	77 (11.4%)	9 (14%)	14 (21%)	91 (9.2%)	59 (11.9%)				
	Diabetes	20 (2.9%)	35 (5.2%)	1 (2%)	3 (5%)	36 (3.6%)	14 (2.8%)				
	Hypertension	99 (14.5%)	99 (14.6%)	3 (5%)	14 (21%)	145 (14.7%)	60 (12.1%)				
	None			54 (82%)	40 (61%)	646 (65.3%)	336 (68.0%)	53 (85.5%)	58 (89.2%)		
Practice Location	Emergency Department	96 (14.1%)	94 (13.9%)	38 (58%)	36 (55%)	417 (42.2%)	190 (38.5%)			48 (12%)	19 (10%)
	Internal Medicine ward			17 (26%)	18 (27%)	98 (9.9%)	56 (11.3%)			31 (8%)	20 (10%)
	ICU/anesthesia			6 (9%)	6 (9%)						
	Labor and delivery			5 (7%)	6 (9%)						
	Ambulance	66 (9.7%)	63 (9.3%)			73 (7.4%)	45 (9.1%)				
	Congregate care setting					46 (4.7%)	20 (4.0%)				
	ICU	48 (7.0%)	59 (8.7%)			184 (18.6%)	85 (17.2%)			37 (10%)	23 (12%)
	Operating room					103 (10.4%)	75 (15.2%)				
	EMS, Fire and Police First Responders									32 (8%)	16 (8%)
Occupation	Nurse	186/677 (27.5%)	167/668 (25.0%)	46 (70%)	42 (64%)						
	Physician	143/677 (21.1%)	144/668 (21.6%)	11 (17%)	16 (24%)						
	Certified Nurse Assistant			2 (3%)	2 (3%)						
	ED Technician			3 (4%)	1 (2%)						
	Respiratory therapist	15/677 (2.2%)	18/668 (2.7%)	3 (4%)	5 (7%)						
	Nurse or Physician							31 (50%)	33 (50.8%)		
	Emergency Medicine Provider					407 (41.1%)	190 (38.5%)				
	ICU provider					160 (16.2%)	83 (16.8%)				
	Anesthesia/ENT					178 (18.0%)	105 (21.3%)				
	HCW in COVID unit					76 (7.7%)	29 (5.9%)				
	Healthcare worker in congregate care setting					11 (1.1%)	4 (0.8%)				
	First responder					115 (11.6%)	65 (13.2%)				

		Vijayaraghavan et al.		Polo et al. (EPICOS)		Llanos-Cuentas et al.		Grau-Pujol et al.		Syed et al.	
		HCQ	Placebo	HCQ[2]	Placebo	HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo
	N (randomization)	213	203	231	223	36	32	142	127	154	46
	Age	32.3 (9.65)	31.8 (8.63)	38 (18-65)	38 (18,65)	39.14 (1.53)	39.28 (1.72)	39.6 (11.2)	40.3 (12.8)	30.25 (NA)	31.9 (9.13)
	Female	100 (46.9%)	97 (47.8%)	149 (64.5%)	143 (64.1%)	20 (55.6%)	20 (62.5%)	104 (73.2%)	93 (73.2%)	68 (44.1%)	23 (50%)
	BMI (kg/m^2)										
	Current smoker	8 (3.8%)	9 (4.4%)					21 (14.9%)	17 (13.8%)	19 (12.3%)	7 (15.2%)
Race/ Ethnicity	White										
	Asian										
	African American										
	Hispanic										
Comorbidities	Asthma	0 (0%)	0 (0%)	20 (8.7%)	9 (4.0%)	3 (8.3%)	4 (12.5%)	5 (3.5%)	2 (1.6%)		
	Diabetes	7 (3.3%)	3 (1.5%)	1 (0.4%)	3 (1.3%)	1 (2.8%)	0 (0%)	0 (0%)	1 (0.8%)	4 (2.6%)	3 (6.5%)
	Hypertension	2 (0.9%)	3 (1.5%)	4 (1.7%)	19 (8.5%)	3 (8.3%)	2 (6.3%)	2 (1.4%)	3 (2.4%)	7 (4.5%)	2 (4.3%)
	None										
Practice Location	Emergency Department	26 (12.2%)	18 (8.9%)	20 (8.7%)	21 (9.4%)						
	Internal Medicine ward	130 (64%)	130 (61%)								
	ICU/anesthesia										
	Labor and delivery										
	Ambulance			0 (0%)	0 (0%)						
	Congregate care setting										
	ICU	53 (24.9%)	53 (26.1%)	17 (7.4%)	13 (5.8%)						
	Operating room										
	EMS, Fire and Police First Responders										
Occupation	Nurse	67 (31.5%)	68 (33.5%)	67 (29.0%)	72 (32.3%)	6 (16.7%)	5 (15.6%)	35 (27.8%)	40 (28.2%)	20 (13.0%)	9 (19.6%)
	Physician	34 (16%)	31 (15.3%)	74 (32%)	66 (29.6%)	23 (63.9%)	16 (50%)	67 (47.2%)	53 (42.1%)	118 (76.6%)	25 (54.3%)
	Certified Nurse Assistant					1 (2.8%)	0 (0%)	12 (8.5%)	12 (9.5%)		
	ED Technician										
	Respiratory therapist										
	Nurse or Physician										
	Emergency Medicine Provider									2 (1.3%)	0 (0%)
	ICU provider										
	Anesthesia/ENT										
	HCW in COVID unit										
	Healthcare worker in congregate care setting										
	First responder									2 (1.3%)	0 (0%)

HCQ=Hydroxychloroquine ; ITT= Intention-to-treat ; BMI=Body mass index ; ICU=Intensive care unit; ED=Emergency department ; ENT=Ear, nose, throat ; HCW=Healthcare worker

[1] More than one HCQ groups with different doses are lumped.

[2] The Polo et al. study randomized participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.

[3] Median (range)

[4] Median (IQR)

[5] Mean (range)

[6] Current or previous smoker

eTable 6. Results of outcome measures in trials included in the meta-analysis. Sample size and the number of participants who had each outcome are reported with proportions (%) in parentheses.

	Treatment	N (ITT)	Confirmed COVID-19	Suspected with COVID compatible symptoms	Adverse event[2]
Naggie et al. (HERO-HCQ)	HCQ	683	3 (0.4)	38 (5.6)	16 (2.3)
	Placebo	676	6 (0.9)	47 (7.0)	13 (1.9)
Abella et al. (PATCH)	HCQ	64	4 (6.3)		29 (45.3)
	Placebo	61	4 (6.6)		17 (27.9)
Rajasingham et al. (MN-COVID-PREP)	HCQ[1]	989	11 (1.1)	47 (4.8)	316 (32.0)
	Placebo	494	6 (1.2)	33 (6.7)	100 (20.2)
Rojas-Serrano et al.	HCQ	62	1 (1.6)		32 (51.6)
	Placebo	65	6 (9.2)		38 (58.5)
McKinnon et al. (WHIP)	HCQ[1]	387	2 (0.5)	22 (5.7)	192 (49.6)
	Placebo	191	2 (1.0)	13 (6.8)	85 (44.5)
Vijayaraghavan et al.	HCQ	211	11 (5.2)	12 (5.7)	21 (10.0)
	Placebo	203	12 (5.9)	12 (5.9)	14 (6.9)
Polo et al. (EPICOS)	HCQ	224	21 (9.4)		100 (44.6)
	Placebo	211	23 (10.9)		94 (44.5)
Llanos-Cuentas et al.	HCQ	34	5 (14.7)		
	Placebo	31	3 (9.7)		
Grau-Pujol et al.	HCQ	137	1 (0.7)	3 (2.2)	53 (38.7)
	Placebo	116	1 (0.9)	3 (2.6)	42 (36.2)
Syed et al.	HCQ[1]	154	42 (27.3)		9 (5.8)
	Placebo	46	7 (15.2)		1 (2.2)

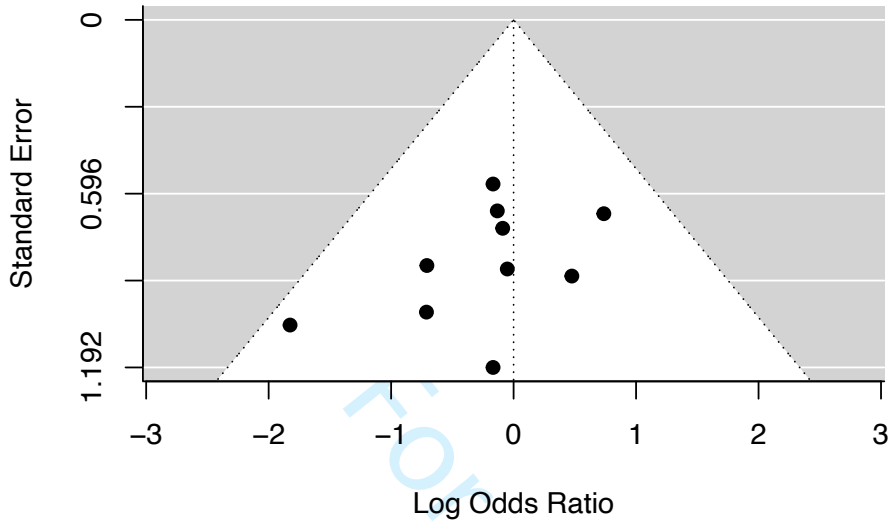
HCQ= Hydroxychloroquine; ITT= Intention-to-treat; AE=Adverse event ; COVID-RS=COVID-19 related symptoms ; Vit C= Vitamin C

[1] More than one HCQ groups with different doses are lumped.

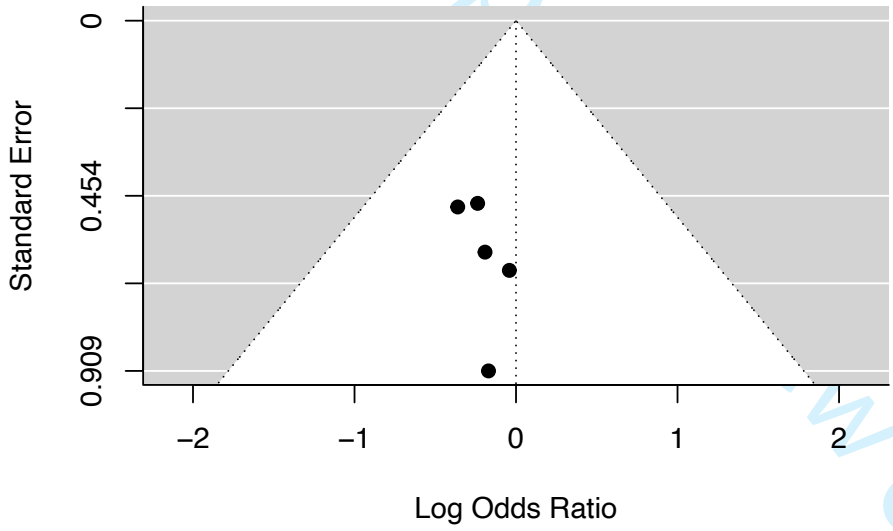
[2] Number of patients with any adverse events

eFigure. Funnel plots for the three outcomes

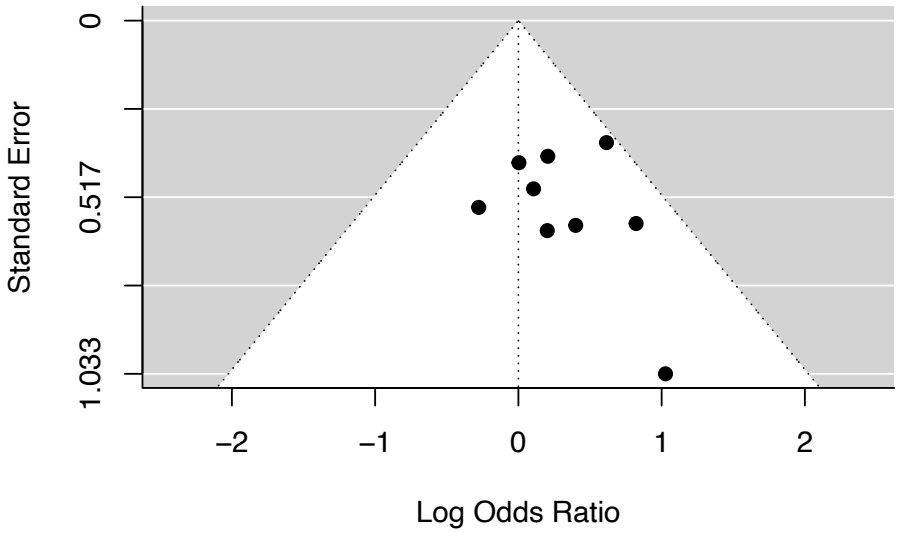
(a) Lab-confirmed positive COVID-19



(b) Suspected COVID-19



(c) Adverse events



eTable 7. GRADE summary of findings table

Outcomes	No of participants (studies) Follow up	Quality of the evidence (GRADE)	Odds ratio (95% Confidence Interval)
Lab-confirmed positive COVID-19	5039 (10 studies) From 28 days to 180 days	⨁⨁⨁⊖ **Moderate**[1] due to imprecision	0.92 (0.58, 1.37)
Suspected COVID-19	4087 (5 studies) From 56 days to 180 days	⨁⨁⨁⊖ **Moderate**[1] due to imprecision	0.78 (0.57, 1.10)
Adverse events	4979 (9 studies) From 56 days to 180 days	⨁⨁⨁⊖ **Moderate**[2] due to imprecision	1.35 (1.03, 1.73)

[1]95% confidence interval includes effect suggesting benefit as well as no benefit.
[2]Although the 95% confidence interval includes an effect suggesting no benefit, we decided to downgrade it by one level because the lower limit is close to the null.

GRADE Working Group grades of evidence is available here:
https://gdt.gradepro.org/app/handbook/handbook.html

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Supplement
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	11-12
Study characteristics	17	Cite each included study and present its characteristics.	8-9, Supplement
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplement
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplement
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11-13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplement
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplement
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14
	23b	Discuss any limitations of the evidence included in the review.	16
	23c	Discuss any limitations of the review processes used.	16
	23d	Discuss implications of the results for practice, policy, and future research.	16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Supplement
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplement

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71